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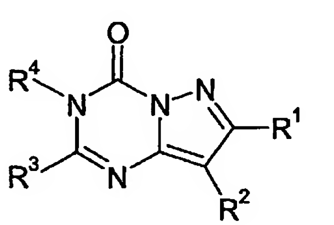
(54) Title: PYRAZOLO'1,5-A!'1,3,5! TRIAZIN-4-ONE DERIVATIVES AS CB1 RECEPTOR ANTAGONISTS



(I)

(57) Abstract: Compounds of Formula (I) are described herein. The compounds have been shown to act as cannabinoid receptor ligands and are therefore useful in the treatment of diseases linked to the mediation of the cannabinoid receptors in animals.

PYRAZOLO '1,5-A!'1,3,5! TRIAZIN -4-ONE DERIVATIVES AS CB1 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to pyrazolo[1,5-a][1,3,5]triazin-4-one compounds. The invention also relates to the use of such compounds as cannabinoid receptor ligands, in particular CB1 receptor antagonists, and uses thereof for treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists.

BACKGROUND

Obesity is a major public health concern because of its increasing prevalence and associated health risks. Obesity and overweight are generally defined by body mass index (BMI), which is correlated with total body fat and estimates the relative risk of disease. BMI is calculated by weight in kilograms divided by height in meters squared (kg/m^2). Overweight is typically defined as a BMI of 25-29.9 kg/m^2, and obesity is typically defined as a BMI of 30 kg/m^2. See, e.g., National Heart, Lung, and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, Washington, DC: U.S. Department of Health and Human Services, NIH publication no. 98-4083 (1998).

The increase in obesity is of concern because of the excessive health risks associated with obesity, including coronary heart disease, strokes, hypertension, type 2 diabetes mellitus, dyslipidemia, sleep apnea, osteoarthritis, gall bladder disease, depression, and certain forms of cancer (e.g., endometrial, breast, prostate, and colon). The negative health consequences of obesity make it the second leading cause of preventable death in the United States and impart a significant economic and psychosocial effect on society. See, McGinnis M, Foege WH., "Actual Causes of Death in the United States," JAMA, **270**, 2207-12 (1993).

Obesity is now recognized as a chronic disease that requires treatment to reduce its associated health risks. Although weight loss is an important treatment outcome, one of the main goals of obesity management

is to improve cardiovascular and metabolic values to reduce obesity-related morbidity and mortality. It has been shown that 5-10% loss of body weight can substantially improve metabolic values, such as blood glucose, blood pressure, and lipid concentrations. Hence, it is believed that a 5-10% intentional reduction in body weight may reduce morbidity and mortality.

Currently available prescription drugs for managing obesity generally reduce weight by inducing satiety or decreasing dietary fat absorption. Satiety is achieved by increasing synaptic levels of norepinephrine, serotonin, or both. For example, stimulation of serotonin receptor subtypes 1B, 1D, and 2C and 1- and 2-adrenergic receptors decreases food intake by regulating satiety. See, Bray GA, "The New Era of Drug Treatment. Pharmacologic Treatment of Obesity: Symposium Overview," Obes Res., **3**(suppl 4), 415s-7s (1995). Adrenergic agents (e.g., diethylpropion, benzphetamine, phendimetrazine, mazindol, and phentermine) act by modulating central norepinephrine and dopamine receptors through the promotion of catecholamine release. Older adrenergic weight-loss drugs (e.g., amphetamine, methamphetamine, and phenmetrazine), which strongly engage in dopamine pathways, are no longer recommended because of the risk of their abuse. Fenfluramine and dexfenfluramine, both serotonergic agents used to regulate appetite, are no longer available for use.

More recently, CB1 cannabinoid receptor antagonists/inverse agonists have been suggested as potential appetite suppressants. See, e.g., Arnone, M., *et al.*, "Selective Inhibition of Sucrose and Ethanol Intake by SR141716, an Antagonist of Central Cannabinoid (CB1) Receptors," Psychopharmacol, **132**, 104-106 (1997); Colombo, G., *et al.*, "Appetite Suppression and Weight Loss after the Cannabinoid Antagonist SR141716," Life Sci., **63**, PL113-PL117 (1998); Simiand, J., *et al.*, "SR141716, a CB1 Cannabinoid Receptor Antagonist, Selectively Reduces Sweet Food Intake in Marmose," Behav. Pharmacol., **9**, 179-181 (1998); and Chaperon, F., *et al.*, "Involvement of Central Cannabinoid (CB1) Receptors in the Establishment of Place Conditioning in Rats," Psychopharmacology, **135**,

324-332 (1998). For a review of cannabinoid CB1 and CB2 receptor modulators, see Pertwee, R.G., "Cannabinoid Receptor Ligands: Clinical and Neuropharmacological Considerations, Relevant to Future Drug Discovery and Development," Exp. Opin. Invest. Drugs, **9**(7), 1553-1571 (2000).

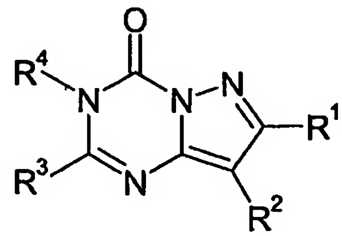
Although investigations are on-going, there still exists a need for a more effective and safe therapeutic treatment for reducing or preventing weight-gain.

In addition to obesity, there also exists an unmet need for treatment of alcohol abuse. Alcoholism affects approximately 10.9 million men and 4.4 million women in the United States. Approximately 100,000 deaths per year have been attributed to alcohol abuse or dependence. Health risks associated with alcoholism include impaired motor control and decision making, cancer, liver disease, birth defects, heart disease, drug/drug interactions, pancreatitis and interpersonal problems. Studies have suggested that endogenous cannabinoid tone plays a critical role in the control of ethanol intake. The endogenous CB1 receptor antagonist SR-141716A has been shown to block voluntary ethanol intake in rats and mice. See, Arnone, M., *et al.*, "Selective Inhibition of Sucrose and Ethanol Intake by SR141716, an Antagonist of Central Cannabinoid (CB1) Receptors," Psychopharmacol, **132**, 104-106 (1997). For a review, see Hungund, B.L and B.S. Basavarajappa, "Are Anadamide and Cannabinoid Receptors involved in Ethanol Tolerance? A Review of the Evidence," Alcohol & Alcoholism. **35**(2) 126-133, 2000.

Current treatments for alcohol abuse or dependence generally suffer from non-compliance or potential hepatotoxicity; therefore, there is a high unmet need for more effective treatment of alcohol abuse/dependence.

SUMMARY

The present invention provides compounds of Formula (I):



(I)

wherein

R^1 is an aryl optionally substituted with one or more substituents, or a heteroaryl optionally substituted with one or more substituents;

R^2 is R^{2a}, $-CH=CH-R^{2a}$, or $-CH_2CH_2-R^{2a}$, where R^{2a} is a chemical moiety selected from (C_1-C_8)alkyl, 3- to 8-membered partially or fully saturated carbocyclic ring(s), 3- to 6-membered partially or fully saturated heterocycle, aryl, or heteroaryl, where said chemical moiety is optionally substituted with one or more substituents;

R^3 is hydrogen or a chemical moiety selected from the group consisting of (C_1-C_4)alkyl, and (C_1-C_4)alkoxy, where said chemical moiety is optionally substituted with one or more substituents,

or R^3 taken together with R^4 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents; and

R^4 is a chemical moiety selected from the group consisting of (C_1-C_8)alkyl, aryl, heteroaryl, aryl(C_1-C_4)alkyl, a 3- to 8-membered partially or fully saturated carbocyclic ring(s), heteroaryl(C_1-C_3)alkyl, 5-6 membered lactone, 5- to 6-membered lactam, and a 3- to 6-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituents,

or R^4 taken together with R^3 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents,

provided that when R^3 is $(C_3\text{-}C_4)$alkyl, R^4 is not (2'-[1-(triphenylmethyl)-1H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl, or (2'-[1H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Preferably, R^1 and R^2 are each independently a chemical moiety selected from phenyl, thiophenyl, pyridyl or pyrimidinyl, where each chemical moiety is substituted with one or more substituents. More preferably, R^1 is a phenyl substituted with one to three substituents independently selected from the group consisting of halo (preferably, chloro or fluoro), $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl (preferably fluoro-substituted alkyl, more preferably, trifluoromethyl) and cyano; and R^2 is a phenyl, pyridyl, thiophenyl, or pyrimidinyl, where the phenyl, the pyridyl, the thiophenyl, and the pyrimidinyl are each substituted with one to three substituents independently selected from the group consisting of halo (preferably, chloro or fluoro), $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl (preferably fluoro-substituted alkyl, more preferably, trifluoromethyl) and cyano. Most preferably, R^1 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, 2-methylphenyl or 2,4-difluorophenyl; and R^2 is 4-chlorophenyl, 4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-bromophenyl, 6-methylpyridin-3-yl, 6-methoxypyridin-3-yl, 5-chloropyridin-2-yl, 5-trifluoromethylpyridin-2-yl, 5-methylpyridin-2-yl, 5-chlorothiophen-2-yl, or 2,4-dimethoxypyrimidin-5-yl.

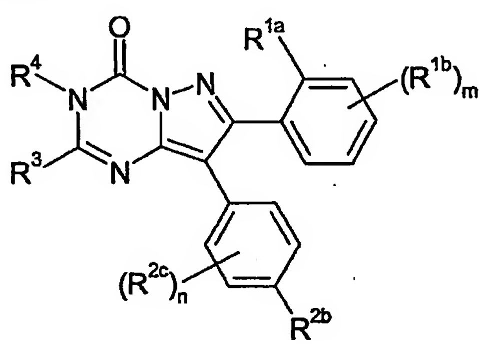
Preferably, R^3 is hydrogen or $(C_1\text{-}C_4)$alkyl, where the $(C_1\text{-}C_4)$alkyl is optionally substituted with one or more substituents, or R^3 taken together with R^4 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents.

More preferably, R^3 is hydrogen, fluoro-substituted $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkyl, wherein the $(C_1\text{-}C_4)$alkyl is optionally substituted with $(C_1\text{-}C_3)$alkylamino, di($(C_1\text{-}C_3)$alkyl)amino, azetidine, pyrrolidine, piperidine, or morpholine, where the $(C_1\text{-}C_3)$ alkyl is optionally substituted with one to three fluorines. Most preferably, R^3 is H, methyl, ethyl or trifluoromethyl.

Preferably, R^4 is a chemical moiety selected from the group consisting of $(C_1\text{-}C_8)$alkyl, aryl$(C_1\text{-}C_4)$alkyl, and 3- to 8-membered partially or fully saturated carbocyclic ring(s), where said chemical moiety is optionally substituted with one or more substituent. More preferably, R^4 is $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl (preferably, fluoro-substituted $(C_1\text{-}C_4)$alkyl), cyclopentyl or cyclohexyl.

Preferred embodiments include any combination of the preferred substituents for R^1, R^2, R^3 and/or R^4 with each other or with any or all of the original definitions for R^1, R^2, R^3 and/or R^4.

In one preferred embodiment of the present invention, a compound of Formula (II) is provided.



(II)

wherein

R^{1a}, R^{1b}, R^{2b}, and R^{2c} are each independently halo, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, or cyano (preferably, R^{1a} is chloro, fluoro, or methyl; R^{1b} is chloro, fluoro or hydrogen (i.e., m is 0); R^{2b} is chloro, fluoro, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, $(C_1\text{-}C_4)$alkoxy, or cyano; and R^{2c} is hydrogen (i.e., n is 0));

n and m are each independently 0, 1 or 2; and

R^3 and R^4 are as defined above (including any combination of the preferred substituents);

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Preferably, R^{1a} is chloro, fluoro, or methyl; R^{1b} is chloro, fluoro, or methyl; R^{2b} is chloro, fluoro, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, $(C_1\text{-}C_4)$alkoxy, or cyano; m is 0 or 1; and n is 0. More preferred embodiments also include any combination of the preferred substituents for R^3 and R^4 discussed above.

Preferred compounds of the present invention include:

7-(2-chlorophenyl)-2-methyl-8-styryl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(2,4-dimethoxypyrimidin-5-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-(2,2-difluoropropyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-(2,2-difluorobutyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(6-methoxypyridin-3-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-ethyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(5-chloropyridin-2-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-2-methyl-3-(2,2,2-trifluoroethyl)-8-(5-trifluoromethylpyridin-2-yl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(5-chlorothiophen-2-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one; and

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-((dimethylamino)methyl)-3-(2,2,2-trifluoroethyl)pyrazolo[1,5-a][1,3,5]triazin-4(3H)-one;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of the compound, or the salt.

Another embodiment of the present invention includes a pharmaceutical composition comprising (1) a compound of the present invention and (2) a pharmaceutically acceptable excipient, diluent, or carrier. Preferably, the composition comprises a therapeutically effective amount of a compound of the present invention. The composition may also contain at least one additional pharmaceutical agent (described herein). Preferred agents include nicotine receptor partial agonists, opioid antagonists (e.g., naltrexone and nalmefene), dopaminergic agents (e.g., apomorphine), attention deficit disorder (ADD including attentin deficit hyperactivity disorder (ADHD)) agents (e.g., Ritalin™, Strattera™, Concerta™ and Adderall™), and anti-obesity agents (described herein below).

In yet another embodiment of the present invention, a method for treating a disease, condition or disorder modulated by a cannabinoid receptor (preferably, a CB1 receptor) antagonists in animals that includes the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of Formula (I), shown above, (or a pharmaceutical composition thereof); wherein

R^1 is an aryl optionally substituted with one or more substituents, or a heteroaryl optionally substituted with one or more substituents;

R^2 is aryl optionally substituted with one or more substituents, heteroaryl optionally substituted with one or more substituents, $-CH=CH-R^{2a}$, or $-CH_2CH_2-R^{2a}$, where R^{2a} is hydrogen or a chemical moiety selected from $(C_1\text{-}C_8)$alkyl, 3- to 8-membered partially or fully saturated carbocyclic

ring(s), 3- to 6-membered partially or fully saturated heterocycle, aryl, heteroaryl, where the chemical moiety is optionally substituted with one or more substituents;

R^3 is hydrogen, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, or (C_1-C_4)alkoxy,

or R^3 taken together with R^4 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents; and

R^4 is a chemical moiety selected from the group consisting of (C_1-C_8)alkyl, aryl, heteroaryl, aryl(C_1-C_4)alkyl, a 3- to 8-membered partially or fully saturated carbocyclic ring(s), heteroaryl(C_1-C_3)alkyl, 5-6 membered lactone, 5- to 6-membered lactam, and a 3- to 6-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituents,

or R^4 taken together with R^3 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Diseases, conditions, and/or disorders modulated by cannabinoid receptor antagonists include eating disorders (e.g., binge eating disorder, anorexia, and bulimia), weight loss or control (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), substance abuse, addictive disorders, impulsivity, alcoholism (e.g., alcohol abuse, addiction and/or dependence including treatment for abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or

dependence including treatment for craving reduction and relapse prevention of tobacco smoking), dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), sexual dysfunction in males (e.g., erectile difficulty), seizure disorders, epilepsy, inflammation, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), attention deficit disorder (including ADHD), Parkinson's disease, and type II diabetes. In a preferred embodiment, the method is used in the treatment of obesity, attention deficit hyperactivity disorder, dementia, alcoholism, and/or tobacco abuse.

Compounds of the present invention may be administered in combination with other pharmaceutical agents. Preferred pharmaceutical agents include nicotine receptor partial agonists, opioid antagonists (e.g., naltrexone (including naltrexone depot), antabuse, and nalmefene), dopaminergic agents (e.g., apomorphine), ADD/ADHD agents (e.g., methylphenidate hydrochloride (e.g., Ritalin™ and Concerta™), atomoxetine (e.g., Strattera™), and amphetamines (e.g., Adderall™)) and anti-obesity agents, such as apo-B/MTP inhibitors, 11β-hydroxy steroid dehydrogenase-1 (11β-HSD type 1) inhibitors, peptide YY_{3-36} or analogs thereof, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine receptor agonists, melanocyte-stimulating hormone receptor analogs, 5-HT2c receptor agonists, melanin concentrating hormone receptor antagonists, leptin, leptin analogs, leptin receptor agonists, galanin receptor antagonists, lipase inhibitors, bombesin receptor agonists, neuropeptide-Y receptor antagonists, thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors, human agouti-related protein antagonists, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, and neuromedin U receptor agonists, and the like.

The combination therapy may be administered as (a) a single pharmaceutical composition which comprises a compound of the present invention, at least one additional pharmaceutical agent described herein and a pharmaceutically acceptable excipient, diluent, or carrier; or (b) two separate pharmaceutical compositions comprising (i) a first composition comprising a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier, and (ii) a second composition comprising at least one additional pharmaceutical agent described herein and a pharmaceutically acceptable excipient, diluent, or carrier. The pharmaceutical compositions may be administered simultaneously or sequentially and in any order.

Yet another aspect of the present invention includes a pharmaceutical kit for use by a consumer to treat diseases, conditions or disorders modulated by cannabinoid receptor antagonists in an animal. The kit comprises a) a suitable dosage form comprising a compound of the present invention; and b) instructions describing a method of using the dosage form to treat diseases, conditions or disorders that are modulated by cannabinoid receptor (in particular, the CB1 receptor) antagonists.

Another embodiment includes a pharmaceutical kit comprising: a) a first dosage form comprising (i) a compound of the present invention and (ii) a pharmaceutically acceptable carrier, excipient or diluent; b) a second dosage form comprising (i) an additional pharmaceutical agent described herein, and (ii) a pharmaceutically acceptable carrier, excipient or diluent; and c) a container.

Definitions

As used herein, the term "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1}. The alkane radical may be straight or branched. For example, the term "(C_1-C_6)alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 6 carbon atoms (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-

methylpentyl, and the like). Similarly, the alkyl portion (i.e., alkyl moiety) of an alkoxy, acyl (e.g., alkanoyl), alkylamino, dialkylamino, and alkylthio group have the same definition as above. When indicated as being "optionally substituted", the alkane radical or alkyl moiety may be unsubstituted or substituted with one or more substituents (generally, one to three substituents except in the case of halogen substituents such as perchloro or perfluoroalkyls) independently selected from the group of substituents listed below in the definition for "substituted." "Halo-substituted alkyl" refers to an alkyl group substituted with one or more halogen atoms (e.g., "fluoro-substituted alkyl" refers to fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 2,2-difluoroethyl, 1,1,1-trifluoroethyl, 2,2,2-trifluoroethyl, 1,1,2-trifluoroethyl, 1,2,2-trifluoroethyl, 1,2,2,2-tetrafluoroethyl, 1,1,2,2-tetrafluoroethyl, 1,1,1,2-tetrafluoroethyl, 1,1,2,2,2-pentafluoroethyl, 1,1,1,2,2-pentafluoroethyl, perfluoroethyl, etc.). Preferred halo-substituted alkyls are the chloro- and fluoro-substituted alkyls, more preferably, fluoro-substituted alkyls. When substituted, the alkane radicals or alkyl moieties are preferably substituted with 1 to 3 fluoro substituents, or 1 or 2 substituents independently selected from $(C_1\text{-}C_3)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_3)$alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, cyano, hydroxy, $(C_1\text{-}C_3)$alkoxy, aryloxy, amino, $(C_1\text{-}C_6)$alkyl amino, di-$(C_1\text{-}C_4)$alkyl amino, aminocarboxylate (i.e., $(C_1\text{-}C_3)$alkyl-O-C(O)-NH-), hydroxy$(C_2\text{-}C_3)$alkylamino, or keto (oxo), and more preferably, 1 to 3 fluoro groups, or 1 substituent selected from $(C_1\text{-}C_3)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, (C_6)aryl, 6-membered-heteroaryl, 3- to 6-membered heterocycle, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_4)$alkyl amino or di-$(C_1\text{-}C_2)$alkyl amino.

The terms "partially or fully saturated carbocyclic ring" (also referred to as "partially or fully saturated cycloalkyl") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiral ring. Unless specified otherwise, the carbocyclic ring is generally a 3- to 8-membered ring. For example, partially or fully saturated carbocyclic rings (or cycloalkyl) include groups such as

cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclpentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, norbornyl (bicyclo[2.2.1]heptyl), norbornenyl, bicyclo[2.2.2]octyl, and the like. When designated as being "optionally substituted", the partially saturated or fully saturated cycloalkyl group may be unsubstituted or substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted." A substituted carbocyclic ring also includes groups wherein the carbocyclic ring is fused to a phenyl ring (e.g., indanyl). The carbocyclic group may be attached to the chemical entity or moiety by any one of the carbon atoms within the carbocyclic ring system. When substituted, the carbocyclic group is preferably substituted with 1 or 2 substituents independently selected from $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_3)$alkenyl, $(C_1\text{-}C_6)$alkylidenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, fluoro, cyano, hydroxy, $(C_1\text{-}C_3)$alkoxy, aryloxy, amino, $(C_1\text{-}C_6)$alkyl amino, di-$(C_1\text{-}C_4)$alkyl amino, aminocarboxylate (i.e., $(C_1\text{-}C_3)$alkyl-O-C(O)-NH-), hydroxy$(C_2\text{-}C_3)$alkylamino, or keto (oxo), and more preferably 1 or 2 from substituents independently selected from $(C_1\text{-}C_2)$alkyl, 3- to 6-membered heterocycle, fluoro, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_4)$alkyl amino or di-$(C_1\text{-}C_2)$alkyl amino. Similarly, any cycloalkyl portion of a group (e.g., cycloalkylalkyl, cycloalkylamino, etc.) has the same definition as above.

The term "partially saturated or fully saturated heterocyclic ring" (also referred to as "partially saturated or fully saturated heterocycle") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiral ring. Unless specified otherwise, the heterocyclic ring is generally a 3- to 6-membered ring containing 1 to 3 heteroatoms (preferably 1 or 2 heteroatoms) independently selected from sulfur, oxygen and/or nitrogen. Partially saturated or fully saturated heterocyclic rings include groups such as epoxy, aziridinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, pyrrolidinyl, N-methylpyrrolidinyl, imidazolidinyl, imidazolinyl, piperidinyl, piperazinyl,

pyrazolidinyl, 2H-pyranyl, 4H-pyranyl, 2H-chromenyl, oxazinyl, morpholino, thiomorpholino, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, and the like. When indicated as being "optionally substituted", the partially saturated or fully saturated heterocycle group may be unsubstiuted or substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted." A substituted heterocyclic ring includes groups wherein the heterocyclic ring is fused to an aryl or heteroaryl ring (e.g., 2,3-dihydrobenzofuranyl, 2,3-dihydroindolyl, 2,3-dihydrobenzothiophenyl, 2,3-dihydrobenzothiazolyl, etc.). When substituted, the heterocycle group is preferably substituted with 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_2-C_4)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, fluoro, cyano, hydroxy, (C_1-C_3)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), or keto (oxo), and more preferably with 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_6)aryl, 6-membered-heteroaryl, 3- to 6-membered heterocycle, or fluoro. The heterocyclic group may be attached to the chemical entity or moiety by any one of the ring atoms within the heterocyclic ring system. Similarly, any heterocycle portion of a group (e.g., heterocycle-substituted alkyl, heterocycle carbonyl, etc.) has the same definition as above.

The term "aryl" or "aromatic carbocyclic ring" refers to aromatic moieties having a single (e.g., phenyl) or a fused ring system (e.g., naphthalene, anthracene, phenanthrene, etc.). A typical aryl group is a 6- to 10-membered aromatic carbocyclic ring(s). When indicated as being "optionally substituted", the aryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) independently selected from the group of substituents listed below in the definition for "substituted." Substituted aryl groups include a chain of aromatic moieties (e.g., biphenyl, terphenyl, phenylnaphthalyl, etc.). When substituted, the aromatic moieties are preferably substituted with 1 or 2

substituents independently selected from (C_1-C_4)alkyl, (C_2-C_3)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, bromo, chloro, fluoro, iodo, cyano, hydroxy, (C_1-C_4)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, or aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), and more preferably, 1 or 2 substituents independently selected from (C_1-C_4)alkyl, chloro, fluoro, cyano, hydroxy, or (C_1-C_4)alkoxy. The aryl group may be attached to the chemical entity or moiety by any one of the carbon atoms within the aromatic ring system. Similarly, the aryl portion (i.e., aromatic moiety) of an aroyl or aroyloxy (i.e., (aryl)-C(O)-O-) has the same definition as above.

The term "heteroaryl" or "heteroaromatic ring" refers to aromatic moieties containing at least one heteratom (e.g., oxygen, sulfur, nitrogen or combinations thereof) within a 5- to 10-membered aromatic ring system (e.g., pyrrolyl, pyridyl, pyrazolyl, indolyl, indazolyl, thienyl, furanyl, benzofuranyl, oxazolyl, imidazolyl, tetrazolyl, triazinyl, pyrimidyl, pyrazinyl, thiazolyl, purinyl, benzimidazolyl, quinolinyl, isoquinolinyl, benzothiophenyl, benzoxazolyl, etc.). The heteroaromatic moiety may consist of a single or fused ring system. A typical single heteroaryl ring is a 5- to 6-membered ring containing one to three heteroatoms independently selected from oxygen, sulfur and nitrogen and a typical fused heteroaryl ring system is a 9- to 10-membered ring system containing one to four heteroatoms independently selected from oxygen, sulfur and nitrogen. When indicated as being "optionally substituted", the heteroaryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) independently selected from the group of substituents listed below in the definition for "substituted." When substituted, the heteroaromatic moieties are preferably substituted with 1 or 2 substituents independently selected from (C_1-C_4)alkyl, (C_2-C_3)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, bromo, chloro, fluoro, iodo, cyano, hydroxy, (C_1-C_4)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, or aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), and more preferably, 1 or

2 substituents independently selected from (C_1-C_4)alkyl, chloro, fluoro, cyano, hydroxy, (C_1-C_4)alkoxy, (C_1-C_4)alkyl amino or di-(C_1-C_2)alkyl amino. The heteroaryl group may be attached to the chemical entity or moiety by any one of the atoms within the aromatic ring system (e.g., imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-5-yl, or pyrid-6-yl). Similarly, the heteroaryl portion (i.e., heteroaromatic moiety) of a heteroaroyl or heteroaryoloxy (i.e., (heteroaryl)-C(O)-O-) has the same definition as above.

The term "acyl" refers to hydrogen, alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, and heteroaryl substituted carbonyl groups. For example, acyl includes groups such as (C_1-C_6)alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, *t*-butylacetyl, etc.), (C_3-C_6)cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, pyrrolid-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, tetrahydrofuranylcarbonyl, etc.), aroyl (e.g., benzoyl) and heteroaroyl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrroyl-2-carbonyl, 1H-pyrroyl-3-carbonyl, benzo[b]thiophenyl-2-carbonyl, etc.). In addition, the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be any one of the groups described in the respective definitions above. When indicated as being "optionally substituted", the acyl group may be unsubstituted or optionally substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted" or the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be substituted as described above in the preferred and more preferred list of substituents, respectively.

The term "substituted" specifically envisions and allows for one or more substitutions that are common in the art. However, it is generally understood by those skilled in the art that the substituents should be

selected so as to not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. Suitable substituents for any of the groups defined above include (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_2-C_6)alkenyl, (C_1-C_6)alkylidenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, halo (e.g., chloro, bromo, iodo and fluoro), cyano, hydroxy, (C_1-C_6)alkoxy, aryloxy, sulfhydryl (mercapto), (C_1-C_6)alkylthio, arylthio, amino, mono- or di-(C_1-C_6)alkyl amino, quaternary ammonium salts, amino(C_1-C_6)alkoxy, aminocarboxylate (i.e., (C_1-C_6)alkyl-O-C(O)-NH-), hydroxy(C_2-C_6)alkylamino, amino(C_1-C_6)alkylthio, cyanoamino, nitro, (C_1-C_6)carbamyl, keto (oxo), acyl, (C_1-C_6)alkyl-CO_2-, glycolyl, glycyl, hydrazino, guanyl, sulfamyl, sulfonyl, sulfinyl, thio(C_1-C_6)alkyl-C(O)-, thio(C_1-C_6)alkyl-CO_2-, and combinations thereof. In the case of substituted combinations, such as "substituted aryl(C_1-C_6)alkyl", either the aryl or the alkyl group may be substituted, or both the aryl and the alkyl groups may be substituted with one or more substituents (typically, one to three substituents except in the case of perhalo substitutions). An aryl or heteroaryl substituted carbocyclic or heterocyclic group may be a fused ring (e.g., indanyl, dihydrobenzofuranyl, dihydroindolyl, etc.).

The term "solvate" refers to a molecular complex of a compound represented by Formula (I) or (II) (including prodrugs and pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC),

benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The term "animal" refers to humans (male or female), companion animals (e.g., dogs, cats and horses), food-source animals, zoo animals, marine animals, birds and other similar animal species. "Edible animals" refers to food-source animals such as cows, pigs, sheep and poultry.

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The terms "treating", "treat", or "treatment" embrace both preventative, i.e., prophylactic, and palliative treatment.

The terms "modulated by a cannabinoid receptor" or "modulation of a cannabinoid receptor" refers to the activation or deactivation of a cannabinoid receptor. For example, a ligand may act as an agonist, partial agonist, inverse agonist, antagonist, or partial antagonist.

The term "antagonist" includes both full antagonists and partial antagonists, as well as inverse agonists.

The term "CB-1 receptor" refers to the G-protein coupled type 1 cannabinoid receptor.

The term "compounds of the present invention" (unless specifically identified otherwise) refer to compounds of Formulae (I) and (II), prodrugs thereof, pharmaceutically acceptable salts of the compounds, and/or prodrugs, and hydrates or solvates of the compounds, salts, and/or prodrugs, as well as, all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds.

DETAILED DESCRIPTION

The present invention provides compounds and pharmaceutical formulations thereof that are useful in the treatment of diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists.

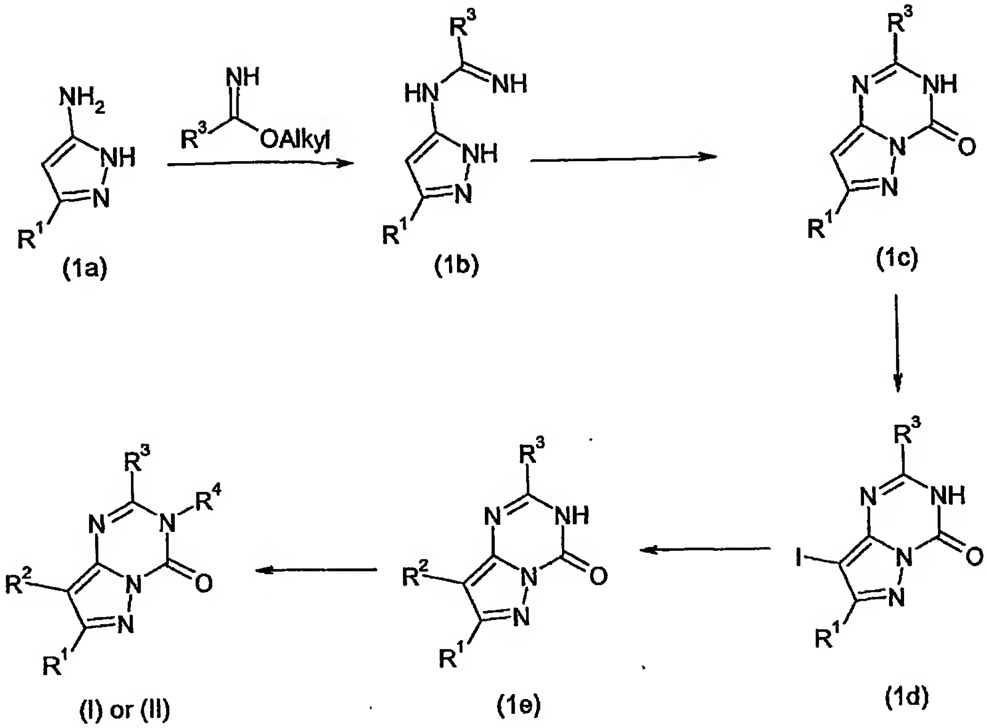
Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in

the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Compounds of Formula (I) and (II) could be prepared using procedures analogous to those previously described in the literature. For example, compounds of Formula (1e) could be prepared analogous to procedures described by He, L., J. Med. Chem., 43, 449-456 (2000) and U.S. Patent No. 3,910,907, incorporated herein by reference. Scheme I outlines the procedures one could use to provide compounds of the present invention *via* pyrazolo-triazinone intermediates (1c), (1d) and (1e).



Scheme I

The 3-aminopyrazole (1a) may be purchased or prepared using procedures analogous to those described in Pakamigawa, A., Yakugaku Zasski, **84**, 1113 (1964). Amidine (1b) may be formed in a reaction inert solvent (e.g., acetonitrile, methylene chloride, chloroform) from the condensation of 3-aminopyrazole (1a) with an alkyl imidate ($R^3C(=NH)OAlkyl$) in the presence or absence of an acid. Suitable alkylimidates include ethyl acetimidate, methyl acetimidate, and ethyl formimidate. Suitable acids include alkanoic acids (e.g., acetic acid, trifluoroacetic acid), sulfonic acids (e.g., benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, sulfuric acid) and hydrochloric acid. Isolation of amidine (1b) as its acetic acid salt is preferred.

Pyrazolotriazinone (1c) may then be formed by treating amidine (1b) with a dialkyl carbonate (e.g., diethyl carbonate or dimethylcarbonate) or dialkyl dithiocarbonate in the presence of base (e.g., sodium methoxide or sodium ethoxide) in a suitable solvent (e.g., methanol or ethanol) at reaction

temperatures from about 30 °C to about 150 °C. Alternatively, pyrazolotriazinone (1c) may be formed by treating amidine (1b) with reagents such as phosgene, triphosgene, or carbonyl diimidazole in the presence or absensce of a base (e.g., triethylamine, diisopropylethyl amine, pyridine, or imidazole) in a reaction inert solvent (e.g., methylene chloride, tetrahydrofuran, diethyl ether, diisopropyl ether, methyl tert-butyl ether or acetonitrile) at reaction temperatures from about –40 °C to about 100 °C.

Alternatively, pyrazolotriazinone (1c, R^3 = H) may be formed by treating 3-aminopyrazole (1a) with 1,3-dimethyl-5-azauracil in the presence of a strong base (e.g., sodium ethoxide) according to procedures described by C.K. Chu et al. in Nucleic Acid Chem., **4**, 19-23 (1991).

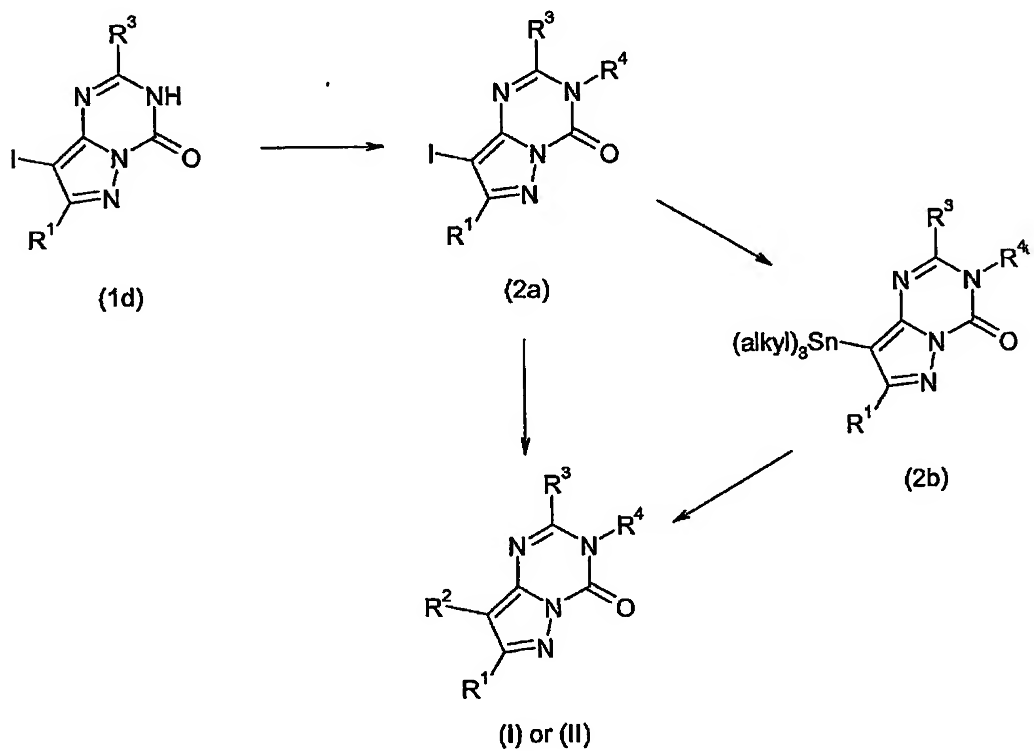
A bromine or iodine may be introduced at the 3-position of pyrazolotriazinone (1c) using procedures analogous to those described in Senga, K., et al., J. Med. Chem., **25**, 243-249 (1982). For example, position 3 may be iodinated by treating the pyrazolotriazinone (1c) with a reagent such as N-iodosuccinimide (NIS), iodine, or iodonium bis-symcollidine perchlorate (preferably NIS) in an aprotic solvent (e.g., carbon tetrachloride, methylene chloride, or chloroform). Suitable reaction temperatures range from about –78 °C to about 30 °C (preferably, about 0 °C).

Intermediate (Ie) may be prepared using procedures analogous to those described for Scheme 17 of U.S. Patent No. 6,372,743 and incorporated herein by reference. For example, the second aryl or heteroaryl group (R^2) is introduced *via* metal-mediated cross-coupling reactions such as the Suzuki reaction (See: A. Suzuki in Metal-Catalyzed Cross-Coupling Reactions; F. Diederich and P.J. Stang, Eds.; Wiley-VCH Verlag, Weinheim, Germany, Chapter 2 (1998) and N. Miyaura and A. Suzuki Chem. Rev., **95**, 2457-2483 (1995)) and the Stille reaction (T.N. Mitchell in Metal-Catalyzed Cross-Coupling Reactions; F. Diederich and P.J. Stang, Eds.; Wiley-VCH Verlag, Weinheim, Germany, Chapter 4 (1998)). In a preferred method, the compound of the Formula (Ie) may be produced by Suzuki reaction of intermediate (1d) with a compound of Formula R^1-$B(OH)_2$

in the presence of a complex or salt of palladium (e.g., $Pd(PPh_3)_4$, $Pd(OAc)_2$, $PdCl_2(dppf)$), a base (e.g., cesium carbonate, sodium carbonate, cesium fluoride, potassium phosphate), and a suitable solvent (e.g., toluene, water, dioxane, N,N-dimethylformamide) in the presence or absence of added ligand (e.g., dppf, dppb). Preferred reaction temperatures range from about 0 °C to about 120 °C (more preferably, from about 80 °C to about 110 °C).

N-Alkylation of intermediate (1e) can then be accomplished using an alkylating agent, such as an alkyl iodide, alkyl triflate, or a substituted benzyl bromide, and a base, preferably cesium carbonate or potassium carbonate, in a polar non-protic solvent such as DMF or THF, at temperatures ranging from about 37 °C to about 150 °C (preferably, from about 20 °C to 40 °C) to provide compounds of Formula (I) or (II).

An alternative preparation of compounds of Formula (I) and (II) is outlined in Scheme II below.



Scheme II

N-alkylation of intermediate (1d) may be accomplished using procedures analogous to the alkylation of (1e) described above. The second aryl or heteroarly group (R^2) may then be introduced by metal-mediated cross-coupling as described above in the preparation of (1e) to provide (I) or (II). The Suzuki and Stille reactions are particularly preferred. Alternatively, intermediate (2a) may be converted to a metal reagent such as stannane (2b) using standard condtions (see V.P. Palle et al. in Bioorg. & Med. Chem. Lett., **12**, 2935-2939 (2002) and references within). Metal-mediated cross-coupling with the appriate aryl or heteraryl derivative (e.g., R^2-Br, R^2-I, or R^2-OTf) would provide (I) or (II).

Conventional methods and/or techniques of separation and purification known to one of ordinary skill in the art can be used to isolate the compounds of the present invention, as well as the various intermediates related thereto. Such techniques will be well-known to one of ordinary skill in the art and may include, for example, all types of chromatography (high pressure liquid chromatography (HPLC), column chromatography using common adsorbents such as silica gel, and thin-layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

The compounds of the present invention may be isolated and used *per se* or in the form of its pharmaceutically acceptable salt, solvate and/or hydrate. The term "salts" refers to inorganic and organic salts of a compound of the present invention. These salts can be prepared *in situ* during the final isolation and purification of a compound, or by separately reacting the compound, N-oxide, or prodrug with a suitable organic or inorganic acid or base and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, hydroiodide, sulfate, bisulfate, nitrate, acetate, trifluoroacetate, oxalate, besylate, palmitiate, pamoate, malonate, stearate, laurate, malate, borate, benzoate, lactate, phosphate, hexafluorophosphate, benzene sulfonate, tosylate, formate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate,

lactobionate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. See, e.g., Berge, et al., *J. Pharm. Sci.*, **66**, 1-19 (1977).

The term "prodrug" means a compound that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

Similarly, if a compound of the present invention contains an alcohol functional group, a prodrug can be formed by the replacement of the

hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $P(O)(O(C_1\text{-}C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a compound of the present invention incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7)cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, -C(OH)C(O)OY' wherein Y' is H, (C_1-C_6)alkyl or benzyl, -C(OY_0)Y_1 wherein Y_0 is (C_1-C_4) alkyl and Y_1 is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl, -C(Y_2)Y_3 wherein Y_2 is H or methyl and Y_3 is mono-N- or di-N,N-(C_1-C_6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

The compounds of the present invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the present invention as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of the present invention incorporates a double bond or a fused ring, both the *cis*- and *trans*- forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography

and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

It is also possible that the compounds of the present invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. For example, all of the tautomeric forms of the aromatic and heteroaromatic moieties are included in the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{123}I, and ^{36}Cl, respectively.

Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and

detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Compounds of the present invention are useful for treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists; therefore, another embodiment of the present invention is a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention and a pharmaceutically acceptable excipient, diluent or carrier.

A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG400, PEG300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other

known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

The present invention further provides a method of treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists in an animal that includes administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition comprising an effective amount of a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier. The method is particularly useful for treating diseases, conditions and/or disorders modulated by cannabinoid receptor (in particular, CB1 receptor) antagonists.

Preliminary investigations have indicated that the following diseases, conditions, and/or disorders are modulated by cannabinoid receptor antagonists: eating disorders (e.g., binge eating disorder, anorexia, and bulimia), weight loss or control (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), substance abuse, addictive disorders, impulsivity, alcoholism (e.g., alcohol abuse, addiction and/or dependence including treatment for abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including treatment for craving reduction and relapse prevention of tobacco smoking), dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), sexual dysfunction in males (e.g., erectile difficulty), seizure disorders, epilepsy, inflammation, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), attention deficit disorder (including ADHD), Parkinson's disease, and type II diabetes.

Accordingly, the compounds of the present invention described herein are useful in treating diseases, conditions, or disorders that are modulated by cannabinoid receptor antagonists. Consequently, the compounds of the present invention (including the compositions and processes used therein) may be used in the manufacture of a medicament for the therapeutic applications described herein.

Other diseases, conditions and/or disorders for which cannabinoid receptor antagonists may be effective include: premenstrual syndrome or late luteal phase syndrome, migraines, panic disorder, anxiety, post-traumatic syndrome, social phobia, cognitive impairment in non-demented individuals, non-amnestic mild cognitive impairment, post operative cognitive

decline, disorders associated with impulsive behaviours (such as, disruptive behaviour disorders (e.g., anxiety/depression, executive function improvement, tic disorders, conduct disorder and/or oppositional defiant disorder), adult personality disorders (e.g., borderline personality disorder and antisocial personality disorder), diseases associated with impulsive behaviours (e.g., substance abuse, paraphilias and self-mutilation), and impulse control disorders (e.g., intermittene explosive disorder, kleptomania, pyromania, pathological gambling, and trichotillomania)), obsessive compulsive disorder, chronic fatigue syndrome, sexual dysfunction in males (e.g., premature ejaculation), sexual dysfunction in females, disorders of sleep (e.g., sleep apnea), autism, mutism, neurodengenerative movement disorders, spinal cord injury, damage of the central nervous system (e.g., trauma), stroke, neurodegenerative diseases or toxic or infective CNS diseases (e.g., encephalitis or meningitis), cardiovascular disorders (e.g., thrombosis), and diabetes.

The compounds of the present invention can be administered to a patient at dosage levels in the range of from about 0.7 mg to about 7,000 mg per day. For a normal adult human having a body weight of about 70 kg, a dosage in the range of from about 0.01 mg to about 100 mg per kilogram body weight is typically sufficient. However, some variability in the general dosage range may be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular compound being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure. It is also noted that the compounds of the present invention can be used in sustained release, controlled release, and delayed release formulations, which forms are also well known to one of ordinary skill in the art.

The compounds of this invention may also be used in conjunction with other pharmaceutical agents for the treatment of the diseases, conditions and/or disorders described herein. Therefore, methods of treatment that

include administering compounds of the present invention in combination with other pharmaceutical agents are also provided. Suitable pharmaceutical agents that may be used in combination with the compounds of the present invention include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, 11β-hydroxy steroid dehydrogenase-1 (11β-HSD type 1) inhibitors, peptide YY_{3-36} or analogs thereof, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine receptor agonists (such as bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT2c receptor agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y receptor antagonists, thyromimetic agents, dehydroepiandrosterone or an analog thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related protein (AGRP) inhibitors, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists and the like. Other anti-obesity agents, including the preferred agents set forth hereinbelow, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

Especially preferred are anti-obesity agents selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin, peptide YY_{3-36} or an analog thereof, and pseudoephedrine. Preferably, compounds of the present invention and combination therapies are administered in conjunction with exercise and a sensible diet.

Representative anti-obesity agents for use in the combinations, pharmaceutical compositions, and methods of the invention can be prepared

using methods known to one of ordinary skill in the art, for example, sibutramine can be prepared as described in U.S. Pat. No. 4,929,629; bromocriptine can be prepared as described in U.S. Pat. Nos. 3,752,814 and 3,752,888; orlistat can be prepared as described in U.S. Pat. Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874; and PYY_{3-36} (including analogs) can be prepared as described in US Publication No. 2002/0141985 and WO 03/027637. All of the above recited references are incorporated herein by reference.

Other suitable pharmaceutical agents that may be administered in combination with the compounds of the present invention include agents designed to treat tobacco abuse (e.g., nicotine receptor partial agonists, bupropion hypochloride (also known under the tradename Zyban™) and nicotine replacement therapies), agents to treat erectile dysfunction (e.g., dopaminergic agents, such as apomorphine), ADD/ADHD agents (e.g., Ritalin™, Strattera™, Concerta™ and Adderall™), and agents to treat alcoholism, such as opioid antagonists (e.g., naltrexone (also known under the tradename ReVia™) and nalmefene), disulfiram (also known under the tradename Antabuse™), and acamprosate (also known under the tradename Campral™)). In addition, agents for reducing alcohol withdrawal symptoms may also be co-administered, such as benzodiazepines, beta-blockers, clonidine, carbamazepine, pregabalin, and gabapentin (Neurontin™). Treatment for alcoholism is preferably administered in combination with behavioral therapy including such components as motivational enhancement therapy, cognitive behavioral therapy, and referral to self-help groups, including Alcohol Anonymous (AA).

Other pharmaceutical agents that may be useful include anti-inflammatory agents (e.g., COX-2 inhibitors); antihypertensive agents; antidepressants (e.g., fluoxetine hydrochloride (Prozac™)); cognitive improvement agents (e.g., donepezil hydrochloride (Aircept™) and other acetylcholinesterase inhibitors); neuroprotective agents (e.g., memantine); antipsychotic medications (e.g., ziprasidone (Geodon™), risperidone

(Risperdal™), and olanzapine (Zyprexa™)); insulin and insulin analogs (e.g., LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH_2; sulfonylureas and analogs thereof: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, Glypizide®, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; α2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linogliride, A-4166; glitazones: ciglitazone, Actos® (pioglitazone), englitazone, troglitazone, darglitazone, Avandia® (BRL49653); fatty acid oxidation inhibitors: clomoxir, etomoxir; α-glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; β-agonists: BRL 35135, BRL 37344, RO 16-8714, ICI D7114, CL 316,243; phosphodiesterase inhibitors: L-386,398; lipid-lowering agents: benfluorex: fenfluramine; vanadate and vanadium complexes (e.g., Naglivan®) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs; antilipolytic agents: nicotinic acid, acipimox, WAG 994, pramlintide (Symlin™), AC 2993, nateglinide, aldose reductase inhibitors (e.g., zopolrestat), glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, sodium-hydrogen exchanger type 1 (NHE-1) inhibitors and/or cholesterol biosynthesis inhibitors or cholesterol absorption inhibitors, especially a HMG-CoA reductase inhibitor, or a HMG-CoA synthase inhibitor, or a HMG-CoA reductase or synthase gene expression inhibitor, a CETP inhibitor, a bile acid sequesterant, a fibrate, an ACAT inhibitor, a squalene synthetase inhibitor, an anti-oxidant or niacin. The compounds of the present invention may also be administered in combination with a naturally occurring compound that acts to lower plasma cholesterol levels. Such naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract, *Hoodia* plant extracts, and niacin.

The dosage of the additional pharmaceutical agent will also be generally dependent upon a number of factors including the health of the

subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired. In general, the dosage range of an anti-obesity agent is in the range of from about 0.001 mg to about 100 mg per kilogram body weight of the individual per day, preferably from about 0.1 mg to about 10 mg per kilogram body weight of the individual per day. However, some variability in the general dosage range may also be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular anti-obesity agent being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is also well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure.

According to the methods of the invention, a compound of the present invention or a combination of a compound of the present invention and at least one additional pharmaceutical agent is administered to a subject in need of such treatment, preferably in the form of a pharmaceutical composition. In the combination aspect of the invention, the compound of the present invention and at least one other pharmaceutical agent may be administered either separately or in the pharmaceutical composition comprising both. It is generally preferred that such administration be oral. However, if the subject being treated is unable to swallow, or oral administration is otherwise impaired or undesirable, parenteral or transdermal administration may be appropriate.

According to the methods of the invention, when a combination of a compound of the present invention and at least one other pharmaceutical agent are administered together, such administration can be sequential in time or simultaneous with the simultaneous method being generally preferred. For sequential administration, a compound of the present invention and the additional pharmaceutical agent can be administered in any order. It is generally preferred that such administration be oral. It is especially preferred that such administration be oral and simultaneous. When a compound of the

present invention and the additional pharmaceutical agent are administered sequentially, the administration of each can be by the same or by different methods.

According to the methods of the invention, a compound of the present invention or a combination of a compound of the present invention and at least one additional pharmaceutical agent (referred to herein as a "combination") is preferably administered in the form of a pharmaceutical composition. Accordingly, a compound of the present invention or a combination can be administered to a patient separately or together in any conventional oral, rectal, transdermal, parenteral, (for example, intravenous, intramuscular, or subcutaneous) intracisternal, intravaginal, intraperitoneal, intravesical, local (for example, powder, ointment or drop), or buccal, or nasal, dosage form.

Compositions suitable for parenteral injection generally include pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Prevention of microorganism contamination of the compositions can be accomplished with various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about

by the use of agents capable of delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, a compound of the present invention or a combination is admixed with at least one inert customary pharmaceutical excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders (e.g., starches, lactose, sucrose, mannitol, silicic acid and the like); (b) binders (e.g., carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, acacia and the like); (c) humectants (e.g., glycerol and the like); (d) disintegrating agents (e.g., agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, sodium carbonate and the like); (e) solution retarders (e.g., paraffin and the like); (f) absorption accelerators (e.g., quaternary ammonium compounds and the like); (g) wetting agents (e.g., cetyl alcohol, glycerol monostearate and the like); (h) adsorbents (e.g., kaolin, bentonite and the like); and/or (i) lubricants (e.g., talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and the like). In the case of capsules and tablets, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be used as fillers in soft or hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the compound of the present invention and/or the additional pharmaceutical agent in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The drug can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the compound of the present invention or the combination, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame seed oil and the like), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the compound of the present invention or the combination, may further comprise suspending agents, e.g., ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal or vaginal administration preferably comprise suppositories, which can be prepared by mixing a compound of the present invention or a combination with suitable non-irritating excipients or carriers, such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ordinary room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity thereby releasing the active component(s).

Dosage forms for topical administration of the compounds of the present invention and combinations of the compounds of the present invention with anti-obesity agents may comprise ointments, powders, sprays and inhalants. The drugs are admixed under sterile conditions with a pharmaceutically acceptable carrier, and any preservatives, buffers, or

propellants that may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also intended to be included within the scope of the present invention.

The following paragraphs describe exemplary formulations, dosages, etc. useful for non-human animals. The administration of the compounds of the present invention and combinations of the compounds of the present invention with anti-obesity agents can be effected orally or non-orally (e.g., by injection).

An amount of a compound of the present invention or combination of a compound of the present invention with an anti-obesity agent is administered such that an effective dose is received. Generally, a daily dose that is administered orally to an animal is between about 0.01 and about 1,000 mg/kg of body weight, preferably between about 0.01 and about 300 mg/kg of body weight.

Conveniently, a compound of the present invention (or combination) can be carried in the drinking water so that a therapeutic dosage of the compound is ingested with the daily water supply. The compound can be directly metered into drinking water, preferably in the form of a liquid, water-soluble concentrate (such as an aqueous solution of a water-soluble salt).

Conveniently, a compound of the present invention (or combination) can also be added directly to the feed, as such, or in the form of an animal feed supplement, also referred to as a premix or concentrate. A premix or concentrate of the compound in a carrier is more commonly employed for the inclusion of the agent in the feed. Suitable carriers are liquid or solid, as desired, such as water, various meals such as alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, corncob meal and corn meal, molasses, urea, bone meal, and mineral mixes such as are commonly employed in poultry feeds. A particularly effective carrier is the respective animal feed itself; that is, a small portion of such feed. The carrier facilitates uniform distribution of the compound in the finished feed with which the premix is blended. Preferably, the compound is thoroughly blended into the

premix and, subsequently, the feed. In this respect, the compound may be dispersed or dissolved in a suitable oily vehicle such as soybean oil, corn oil, cottonseed oil, and the like, or in a volatile organic solvent and then blended with the carrier. It will be appreciated that the proportions of compound in the concentrate are capable of wide variation since the amount of the compound in the finished feed may be adjusted by blending the appropriate proportion of premix with the feed to obtain a desired level of compound.

High potency concentrates may be blended by the feed manufacturer with proteinaceous carrier such as soybean oil meal and other meals, as described above, to produce concentrated supplements, which are suitable for direct feeding to animals. In such instances, the animals are permitted to consume the usual diet. Alternatively, such concentrated supplements may be added directly to the feed to produce a nutritionally balanced, finished feed containing a therapeutically effective level of a compound of the present invention. The mixtures are thoroughly blended by standard procedures, such as in a twin shell blender, to ensure homogeneity.

If the supplement is used as a top dressing for the feed, it likewise helps to ensure uniformity of distribution of the compound across the top of the dressed feed.

Drinking water and feed effective for increasing lean meat deposition and for improving lean meat to fat ratio are generally prepared by mixing a compound of the present invention with a sufficient amount of animal feed to provide from about 10^{-3} to about 500 ppm of the compound in the feed or water.

The preferred medicated swine, cattle, sheep and goat feed generally contain from about 1 to about 400 grams of a compound of the present invention (or combination) per ton of feed, the optimum amount for these animals usually being about 50 to about 300 grams per ton of feed.

The preferred poultry and domestic pet feeds usually contain about 1 to about 400 grams and preferably about 10 to about 400 grams of a compound of the present invention (or combination) per ton of feed.

For parenteral administration in animals, the compounds of the present invention (or combination) may be prepared in the form of a paste or a pellet and administered as an implant, usually under the skin of the head or ear of the animal in which increase in lean meat deposition and improvement in lean meat to fat ratio is sought.

In general, parenteral administration involves injection of a sufficient amount of a compound of the present invention (or combination) to provide the animal with about 0.01 to about 20 mg/kg/day of body weight of the drug. The preferred dosage for poultry, swine, cattle, sheep, goats and domestic pets is in the range of from about 0.05 to about 10 mg/kg/day of body weight of drug.

Paste formulations can be prepared by dispersing the drug in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

Pellets containing an effective amount of a compound of the present invention, pharmaceutical composition, or combination can be prepared by admixing a compound of the present invention or combination with a diluent such as carbowax, carnuba wax, and the like, and a lubricant, such as magnesium or calcium stearate, can be added to improve the pelleting process.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increase in lean meat deposition and improvement in lean meat to fat ratio desired. Moreover, implants may also be made periodically during the animal treatment period in order to maintain the proper drug level in the animal's body.

The present invention has several advantageous veterinary features. For the pet owner or veterinarian who wishes to increase leanness and/or trim unwanted fat from pet animals, the instant invention provides the means by which this may be accomplished. For poultry, beef, and swine breeders,

utilization of the method of the present invention yields leaner animals that command higher sale prices from the meat industry.

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

Unless specified otherwise, starting materials are generally available from commercial sources such as Aldrich Chemicals Co. (Milwaukee, WI), Lancaster Synthesis, Inc. (Windham, NH), Acros Organics (Fairlawn, NJ), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, NJ), and AstraZeneca Pharmaceuticals (London, England).

General Experimental Procedures

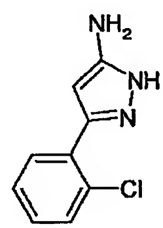
NMR spectra were recorded on a Varian Unity™ 400 (available from Varian Inc., Palo Alto, CA) at room temperature at 400 MHz for proton. Chemical shifts are expressed in parts per million (δ) relative to residual solvent as an internal reference. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; 2s, two singlets. Atmospheric pressure chemical ionization mass spectra (APCI) were obtained on a Fisons™ Platform II Spectrometer (carrier gas: acetonitrile: available from Micromass Ltd, Manchester, UK). Chemical ionization mass spectra (CI) were obtained on a Hewlett-Packard™ 5989 instrument (ammonia ionization, PBMS: available from Hewlett-Packard Company, Palo Alto, CA). Electrospray ionization mass spectra (ES) were obtained on a Waters™ ZMD instrument (carrier gas: acetonitrile: available from Waters Corp., Milford, MA). Where the intensity of chlorine or bromine-containing ions are described, the expected intensity ratio was observed (approximately 3:1 for $^{35}Cl/^{37}Cl$-containing ions and 1:1 for $^{79}Br/^{81}Br$-containing ions) and the intensity of only the lower mass ion is given. In some cases only representative ^{1}H NMR peaks are given. MS peaks are reported for all

examples. Optical rotations were determined on a PerkinElmer™ 241 polarimeter (available from PerkinElmer Inc., Wellesley, MA) using the sodium D line (λ = 589 nm) at the indicated temperature and are reported as follows $[\alpha]_D^{temp}$, concentration (c = g/100 ml), and solvent.

Column chromatography was performed with either Baker™ silica gel (40 µm; J.T. Baker, Phillipsburg, NJ) or Silica Gel 50 (EM Sciences™, Gibbstown, NJ) in glass columns or in Flash 40 Biotage™ columns (ISC, Inc., Shelton, CT) under low nitrogen pressure.

Preparation of Key Intermediates

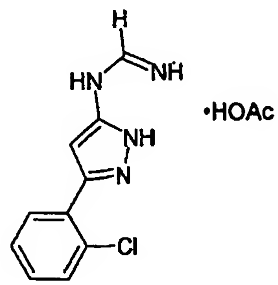
Preparation of Intermediate 5-(2-Chlorophenyl)-2H-pyrazol-3-ylamine (I-1A-1a):



I-1A-1a

A solution of 2-chlorobenzoylacetonitrile (15.9 g, 89 mmol) and hydrazine hydrate (8.9 g, 0.18 mol) in ethanol (2 ml) was heated at reflux for 22 hr. After cooling to room temperature, the reaction was concentrated, *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, dried ($MgSO_4$), and concentrated, *in vacuo*, to a brown oil. Flash chromatography using 10% ethyl acetate in methylene chloride, changing to 5% methanol in methylene chloride as eluant afforded title product I-1A-1a (17.3 g, quantitative): +ESI MS (M+1) 194.2; ^{1}H NMR (400 MHz, CD_3OD) δ 7.60-7.25 (m, 4H), 5.99 (br s, 1H).

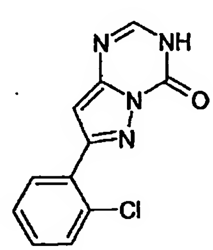
Preparation of Intermediate N-[5-(2-Chlorophenyl)-2H-pyrazol-3-yl]-formamidine, Acetate Salt (I-1A-1b):



I-1A-1b

To a vigorously stirred solution of saturated aqueous Na_2CO_3 (50 mL) and methylene chloride (50 ml) was added solid ethylformimidate hydrochloride salt (8.98 g, 82 mol). After stirring for several minutes the aqueous layer was separated and extracted with additional methylene chloride (3 x 50 ml). The combined organic layers were dried ($MgSO_4$) and filtered. To the stirred solution was added 5-(2-chlorophenyl)-2H-pyrazol-3-ylamine (I-1A-1a; 5.27 g, 27 mmol) in methylene chloride (50 mL) and then glacial acetic acid (2.67 ml, 46.6 mmol), dropwise. The cloudy precipitate began to form as the acetic acid was added. After stirring overnight, the solids were collected by vacuum filtration and washed with methylene chloride. After drying, *in vacuo*, intermediate I-1A-1b, contaminated with ~25% the corresponding dimer (MW = 396; 2 pyrazoles + 1 formamidine) was obtained as a solid (5.7 g, 75%): +APcl MS (M+1) 221.1; ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (s, 1H), 7.62-7.30 (m, 4H), 6.48 (s, 1H), 1.92 (s, 3H).

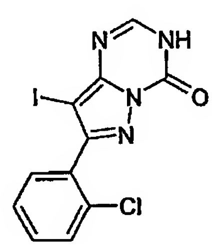
Preparation of Intermediate 7-(2-Chlorophenyl)- 3H-pyrazolo[1,5-a][1,3,5]-triazin-4-one (I-1A-1c):



I-1A-1c

To an ethanolic solution of sodium ethoxide, generated by portionwise addition of sodium metal (4.2 g, 455 mmol) to stirred ethanol (250 ml), was added *N*-[5-(2-chlorophenyl)-2H-pyrazol-3-yl]-formamidine, acetate salt (I-1A-1b; 5.2 g, 18.5 mmol) in one portion. Diethyl carbonate (44.1 ml, 364 mmol) was added, dropwise, and the mixture was heated at reflux for 2 hours. After cooling to room temperature, the reaction was concentrated, *in vacuo*, and then extracted with ethyl acetate from water, adjusted to pH 7 with 3 M aqueous HCL. The combined organic layers were washed with water and then brine, dried ($MgSO_4$), filtered, and then concentrated, *in vacuo*, to one-third volume at which time a precipitate began to form. After stirring overnight, the product was collected by vacuum filtration and then dried, *in vacuo*, to afford I-1A-1c as a solid (2.61 g, 57%). A second crop of the intermediate was collected from the filtrate after standing an additional 24 hours (600 mg, 19%): +ESI MS (M+1) 247.1; ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (s, 1H), 7.86-7.82 (m, 1H), 7.55-7.51 (m, 1H), 7.45-7.39 (m, 2H), 6.92 (s, 1H).

Preparation of Intermediate 7-(2-Chlorophenyl)-8-iodo-3H-pyrazolo[1,5-a]-[1,3,5]triazin-4-one (I-1A-1d):

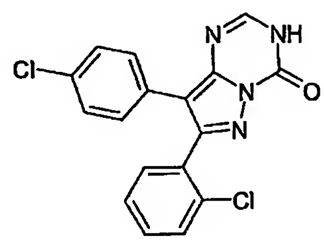


I-1A-1d

To a suspension of 7-(2-chlorophenyl)-3H-pyrazolo[1,5-a][1,3,5]-triazin-4-one (I-1A-1c; 2.59 g, 10.5 mmol) in chloroform (115 ml) cooled in an ice bath was added *N*-iodosuccinimide (2.36 g, 10.5 mmol), portionwise, over 15 minutes. After stirring for 3 hours, the reaction was added to stirring water and methylene chloride. A solution of saturated aqueous $Na_2S_2O_4$

was added until the color remained light yellow. The solid precipitate that was dispersed in the aqueous phase was collected by vacuum filtration and then dried, *in vacuo*, to afford intermediate I-1A-1d as a solid (3.78 g, 97%): +APcl MS (M+1) 372.9; ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.55-7.40 (m, 4H).

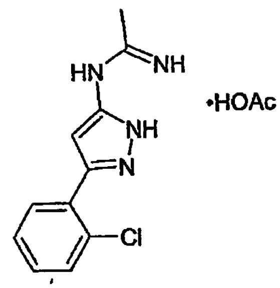
Preparation of Intermediate 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-1e):



I-1A-1e

A mixture of 7-(2-chlorophenyl)-8-iodo-3H-pyrazolo[1,5-a][1,3,5]-triazin-4-one (I-1A-1d; 500 mg, 1.34 mmol), 4-chlorophenylboronic acid (315 mg, 2.01 mmol), and tetrakis(triphenylphosphine)palladium (50 mg, 0.043 mmol) under an argon atmosphere in ethanol (12 ml) and 2M aqueous Na_2CO_3 (2.5 ml) was degassed (3X) by pulling a vacuum followed by refilling with argon gas. The mixture was heated at 68 °C for 7 hours and then cooled to room temperature. The mixture was extracted from water with ethyl acetate, the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated, *in vacuo*, to afford a dark, viscous oil (690 mg). The product was crystallized from methanol and then collected by vacuum filtration to afford, after rinsing with methanol, intermediate I-1A-1e (218 mg, 45%) as a solid: +APcl MS (M+1) 357.0; ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (s, 1H), 7.54-7.41 (m, 4H), 7.34 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H).

Preparation of Intermediate N-[5-(2-Chlorophenyl)-2H-pyrazol-3-yl]-acetamidine, Acetate Salt (I-1A-3a):



I-1A-3a

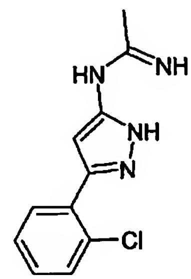
To a solution of 2-chlorobenzoylacetonitrile (400 g, 2.23 mol) in ethanol (9 L) was added hydrazine hydrate (221 g, 4.42 mol) over 15 minutes while maintaining internal reaction temperature at 15 to 25 °C. The mixture was then heated at 75 °C for 20 hr. After cooling, the reaction was concentrated, *in vacuo*, to give a brown oil. The residue was dissolved in ethyl acetate (4 L), washed with half saturated brine (4 L), and then dried (Na_2SO_4) to a give a crude, dark orange solution of 5-(2-chlorophenyl)-2H-pyrazol-3-ylamine that was carried directly into the next reaction: +ESI MS (M+1) 194.0..

To a stirred solution of potassium carbonate (2 Kg) in water (5 L) was added solid ethyl acetimidate hydrochloride salt (731 g, 5.83 mol), portionwise, over 10 minutes. The ethyl acetimidate free base was extracted into ethyl acetate (4 L), separated and the organic layer then dried (Na_2SO_4).

To the stirred ethyl acetate solution of 5-(2-chlorophenyl)-2H-pyrazol-3-ylamine (I-1A-1a) was added the ethyl acetimidate free base solution over 10 minutes. Glacial acetic acid (140 ml, 2.42 mol) was then added over a 20-minute period while maintaining the reaction between 10 and 30 °C. A precipitate began to form after approximately 15 ml of acetic acid had been added. After stirring for 5 hours, the product was collected on a course sintered glass funnel. The product on the filter was washed with ethyl acetate until the eluant was colorless. After drying overnight on the frit under a stream of air using low vacuum, intermediate I-1A-3a was obtained as an off-white, crystalline solid (543 g, 82.6%): +ESI MS (M+1) 235.1; ^{1}H NMR

(400 MHz, CD_3OD) δ 7.58-7.52 (m, 2H), 7.42-7.39 (m, 2H), 6.43 (s, 1H), 2.38 (s, 3H), 1.86 (s, 3H).

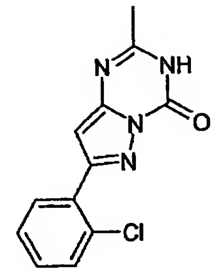
Preparation of Intermediate N-[5-(2-Chlorophenyl)-2H-pyrazol-3-yl]-acetamidine (I-1A-3b):



I-1A-3b

To a stirred mixture of 2 M aqueous NaOH (75 mL, 152 mol) and 2-methyltetrahydrofuran (155 ml) was added N-[5-(2-chlorophenyl)-2H-pyrazol-3-yl]-acetamidine, acetate salt (I-1A-3a; 11.5 g, 39.0 mmol), portionwise, over 15 minutes at room temperature. The organic layer was separated, washed with brine (75 ml), and then concentrated to one half volume, at which time a precipitate begins to form. The stirred mixture was diluted with MTBE (70 mL), cooled to –5 °C in an ice/brine bath for 1 hour, and the resulting precipitate collected on a course sintered glass funnel. The solid was washed with ice cold MTBE (50 mL) and then dried, *in vacuo*, to afford intermediate I-1A-3b as a solid (5.74 g, 63%): +ESI MS (M+1) 235.3; ^{1}H NMR (400 MHz, CD_3OD) δ 7.56-7.53 (m, 1H), 7.48-7.44 (m, 1H), 7.36-7.28 (m, 2H), 6.27 (s, 1H), 2.04 (s, 3H).

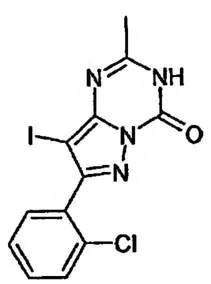
Preparation of Intermediate 7-(2-Chlorophenyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3c):



I-1A-3c

To a pale yellow solution of *N*-[5-(2-chlorophenyl)-2H-pyrazol-3-yl]-acetamidine (I-1A-3b; 2.04 g, 8.69 mmol) in DMSO (17 mL) was added 1,1'-carbonyldiimidazole (1.53 g, 9.44 mmol), portionwise over 1 minute at room temperature. After stirring for one hour, the reaction was added to stirred 1 M aqueous HCl (17 ml) over 5 minutes. The colorless precipitate that formed was stirred for 2.5 hours and then collected on a course sintered funnel. The solids were washed with water (50 ml) and then dried on the frit under a stream of air using low vacuum to afford I-1A-3c as a colorless solid (2.29 g, quantitative): +APcl MS (M+1) 261.3; ^{1}H NMR (400 MHz, CD_3OD) δ 7.84-7.81 (m, 1H), 7.54-7.51 (m, 1H), 7.44-7.38 (m, 2H), 6.77 (s, 1H), 2.42 (s, 3H).

Preparation of Intermediate 7-(2-Chlorophenyl)-8-iodo-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3d):

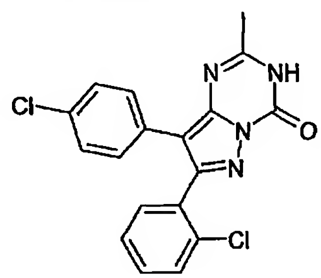


I-1A-3d

To a suspension of 7-(2-chlorophenyl)-2-methyl-3H-pyrazolo[1,5-a]-[1,3,5]triazin-4-one (I-1A-3c; 18.9 g, 72.6 mmol) in methylene chloride (290 ml) cooled in an ice bath was added *N*-iodosuccinimide (18.0 g, 79.9 mmol).

The mixture became homogeneous orange solution within 5 minutes. After stirring for 5 hours, the mixture was washed with 50% saturated aqueous NH_4OH (160 ml), 1 M aqueous $Na_2S_2O_3$ (120 ml), and brine (120 ml). The solution was concentrated, *in vacuo*, and then concentrated again from MTBE (150 ml). Additional MTBE (75 ml) was added and stirred for 1 hour. The resulting solid precipitate was collected by vacuum filtration in a course sintered glass funnel, washed with MTBE (50 ml) and then dried, *in vacuo*, to afford product I-1A-3d as a solid (25.5 g, 91%): +APcl MS (M+1) 387.3; ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (d, J = 7.1 Hz, 1H), 7.51-7.39 (m, 3H), 2.45 (s, 3H).

Preparation of Intermediate 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3e):

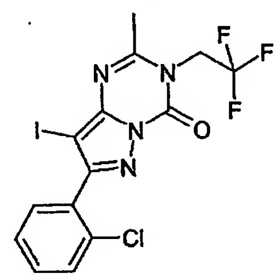


I-1A-3e

To a mixture of 7-(2-chlorophenyl)-8-iodo-2-methyl-3H-pyrazolo-[1,5-a][1,3,5]triazin-4-one (I-1A-1d; 141 g, 364 mmol) and 4-chlorophenyl-boronic acid (85.1 g, 544 mmol) in dimethoxyethane (1.4 L) was added 2 M aqueous Na_2CO_3 (365 ml) and then (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II), dichloromethane complex (5.80 g, 7.17 mmol). The reaction was heated at reflux for 16 hours, cooled, and the organic layer separated and then concentrated under reduced pressure. The residue was dissolved in methyltetrahydrofuran (1.4 L) and washed with 1 M aqueous NaOH (2 X 700 ml) and 1 M aqueous HCl (700 ml). The solvent was removed, *in vacuo*, to give a brown solid which was suspended in methanol (1.2 L). The mixture was concentrated to one-third volume, the solids were

collected by vacuum filtration in a course sintered glass funnel, washed with methanol (1 L) and then dried, *in vacuo*, to afford product I-1A-3e as a light-brown solid (103 g, 76%): +APcl MS (M+1) 371.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 7.54-7.43 (m, 4H), 7.35-7.26 (m, 4H), 2.35 (s, 3H).

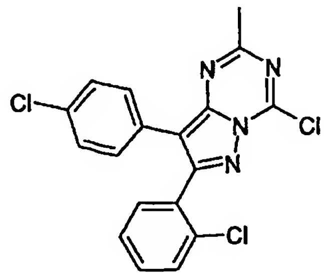
Preparation of Intermediate 7-(2-Chlorophenyl)-8-iodo-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-6A-1a):



I-6A-1a

To a solution of 7-(2-chlorophenyl)-8-iodo-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3d; 5.00 g, 12.9 mmol) in dimethylformamide (12 ml) was added Cs_2CO_3 (4.20 g, 12.9 mmol) and then trifluoromethane-sulfonic acid 2,2,2-trifluoroethyl ester (3.00 g, 12.9 mmol). After stirring overnight, the mixture was extracted from water with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and then concentrated, *in vacuo*, to afford the crude product. Crystallization of the crude product from diethyl ether afforded I-6A-1a (4.82 g, 80%) as a solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.65-7.48 (m, 4H), 5.07 (q, J = 8.7 Hz, 2H), 2.78 (s, 3H).

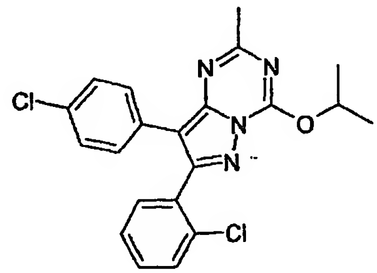
Preparation of Intermediate 4-Chloro-7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazine (I-8A-1a):



I-8A-1a

To a stirred slurry of 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3e; 30.0 g, 80.8 mmol) in toluene (400 ml) at room temperature was added diisopropylethylamine (30.3 ml, 173 mmol) and then $POCl_3$ (15.9 ml, 168 mmol) over 10 minutes. The mixture was heated at 80 °C for 5 hours, cooled to room temperature, and then slowly quenched by slow addition to half saturated brine (300 ml). The biphasic mixture was filtered through Celite® to remove the brown solids that formed on quench. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (200 ml) and then brine (200 ml). The organic solution was concentrated, *in vacuo*, to ½ volume and then filtered through a cotton plug. The solution was further concentrated to ¼ volume, at which point, a yellow solid began to precipitate. Hexane (300 ml) was then added and stirred for 1 hour. The solids were collected on a sintered glass funnel and dried, *in vacuo*, to afford the desired product I-8A-1a (22.3 g, 71%) as a dark-yellow solid: +APcI MS (M+1) 389.1; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.50-7.39 (m, 6H), 7.28 (d, J = 8.7 Hz, 2H), 2.73 (s, 3H).

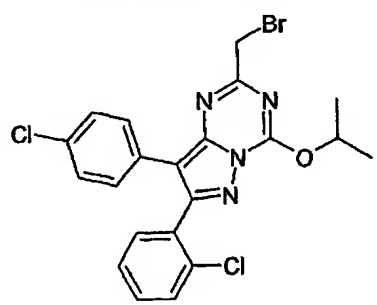
Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-4-isopropoxy-2-methylpyrazolo[1,5-a][1,3,5]triazine (I-8A-1b):



I-8A-1b

To a suspension of 4-chloro-7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazine (I-8A-1a; 300 mg, 0.77 mmol) in isopropanol 15 ml) was added solid $NaHCO_3$ (260 mg, 3.1 mmol), and the mixture was heated at 80 °C for 20 hours. After cooling, the suspended solids were collected by filtration and the filtrate was concentrated, *in vacuo*, to give additional solids. The combined solids were then purified on a Biotage™ Flash 40S column using 10-20% ethyl acetate in hexanes to afford I-8A-1b (225 mg, 71%) as an off-white solid: +ESI MS (M+1) 413.4; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.50-7.34 (m, 6H), 7.24 (d, J = 8.7 Hz, 2H), 5.73 (septuplet, J = 6.2 Hz, 1H), 2.62 (s, 3H), 1.55 (d, J = 6.2 Hz, 6H).

Preparation of 2-(Bromomethyl)-7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-isopropoxypyrazolo[1,5-a][1,3,5]triazine (I-8A-1c):

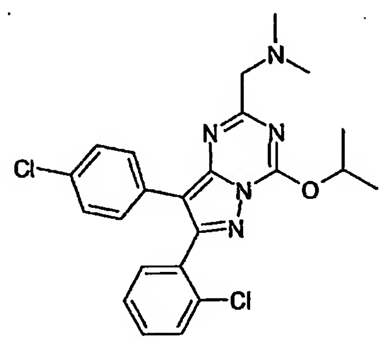


I-8A-1c

A mixture of 7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-isopropoxy-2-methylpyrazolo[1,5-a][1,3,5]triazine (I-8A-1b; 201 mg, 0.49 mmol), N-

bromosuccinimide (96 mg, 0.54 mmol), and azobisisobutyronitrile (20 mg, 0.12 mmol) in carbon tetrachloride (5 ml) was heated at 80 °C for 12 hours. The reaction was cooled, concentrated, *in vacuo*, and then purified on a Biotage™ Flash 12M column using 3:2 methylene chloride/hexanes to afford I-8A-1c (73 mg, 30%) as a solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.56-7.44 (m, 4H), 7.41 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 5.76 (septuplet, J = 6.2 Hz, 1H), 4.53 (s, 2H), 1.57 (d, J = 6.2 Hz, 6H).

Preparation of (7-(2-Chlorophenyl)-8-(4-chlorophenyl)-4-isopropoxypyrazolo[1,5-a][1,3,5]triazin-2-yl)-N,N-dimethylmethanamine (I-8A-1d):

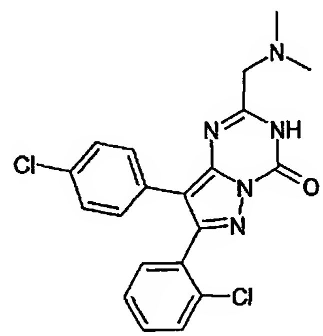


I-8A-1d

To a 0 °C solution of 2-(bromomethyl)-7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-isopropoxypyrazolo[1,5-a][1,3,5]triazine (I-8A-1c; 63 mg, 0.13 mmol) and diisopropylethylamine (25 µl, 0.14 mmol) in DMF (1.5 ml) was added dimethylamine (77 µl, 0.15 mmol). After 15 minutes, TLC indicated the reaction to be complete. The reaction was warmed to room temperature, stirred overnight, and then extracted from water with ethyl acetate. The combined organic layers were washed with water and brine (200 ml), dried ($MgSO_4$) and then concentrated, in vacuo. The residue was purified on a Chromatotron using 1-10% methanol in methylene chloride to afford I-8A-1d (32 mg, 55%) as a solid: +ESI MS (M+1) 456.0; ^{1}H NMR (400 MHz, CD_3OD) δ 7.54-7.44 (m, 4H), 7.43 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7

Hz, 2H), 5.82 (septuplet, J = 6.2 Hz, 1H), 3.75 (s, 2H), 2.47 (s, 6), 1.55 (d, J = 6.2 Hz, 6H).

Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-((dimethylamino)methyl)pyrazolo[1,5-a][1,3,5]triazin-4(3H)-one (I-8A-1e):

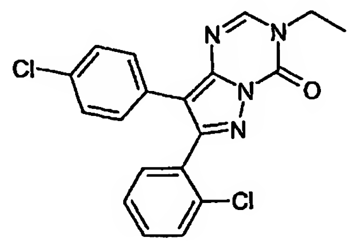


I-8A-1e

To a 0 °C solution of (7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-isopropoxypyrazolo[1,5-a][1,3,5]triazin-2-yl)-N,N-dimethylmethanamine (I-8A-1d; 20 mg, 0.044 mmol) in methanol (1 ml) was added 1M HCl in ether (88 μl, 0.088 mmol). After stirring 10 minutes, the reaction was warmed to room temperature over 10 minutes and then concentrated, in vacuo. The residue was purified on a Chromatotron using 20-9:1:0.05 methylene chloride/methanol/NH_4OH to afford I-8A-1e (4.7 mg, 26%) as a solid: ^1H NMR (400 MHz, CD_3OD) δ 7.52-7.38 (m, 4H), 7.36 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 4.05 (s, 2H), 2.88 (s, 6).

Example 1

Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-3-ethyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (1A-1):

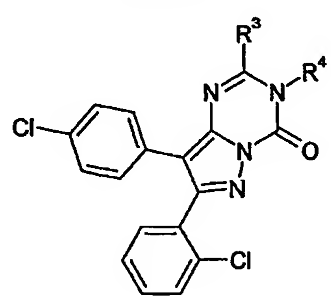


1A-1

To a solution of 7-(2-chlorophenyl)-8-(4-chlorophenyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-1e; 40 mg, 0.11 mmol) in dimethylformamide (1 ml) was added Cs_2CO_3 (39 mg, 0.12 mmol) and ethyl iodide (19 mg, 0.12 mmol). After stirring overnight, the mixture was extracted from water with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and then concentrated, *in vacuo*, to afford the crude product. Purification on a Biotage™ Flash 12S column using 2:3 ethyl acetate in hexanes as eluant afforded 1A-1 (33 mg, 76%) as a solid: +APcI MS (M+1) 385.1; ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 7.53-7.41 (m, 4H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 4.14 (q, *J* = 7.5 Hz, 2H), 1.45 (t, *J* = 7.3 Hz, 3H).

The compounds listed in Table 1 below were prepared using procedures analogous to those described above for the synthesis of Compound 1A-1 using the appropriate starting materials which are available commercially, prepared using preparations well-known to those skilled in the art, or prepared in a manner analogous to routes described above for other intermediates.

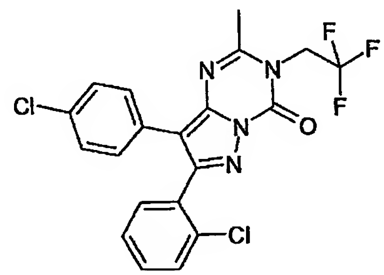
Table 1



Example No.	$-R^3$	$-R^4$	MS $(M+H)^+$
1A-2	H	Me	371.1
1A-3	Me	Et	399.2
1A-4	Me	Me	385.1

Example 2

Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (2A-1):



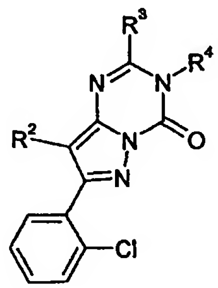
2A-1

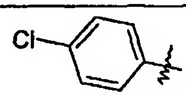
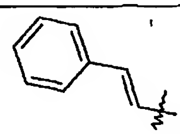
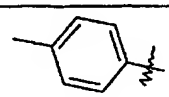
To a solution of 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3e; 65 mg, 0.18 mmol) in dimethylformamide (1.5 ml) was added Cs_2CO_3 (57 mg, 0.18 mmol) and trifluoromethanesulfonic acid 2,2,2-trifluoroethyl ester (41 mg, 0.18 mmol). After stirring overnight, the mixture was extracted from water with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and then concentrated, *in vacuo*, to afford the crude product. Purification on a Chromatotron using 4% ethyl acetate in methylene chloride as eluant afforded 2A-1 (61 mg, 82%) as a solid: +ESI MS (M+1) 453.3; ^1H NMR (400 MHz, DMSO-d_6) δ 7.56-7.44 (m, 4H), 7.35 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.9 Hz, 2H), 5.05 (q, J = 8.7 Hz, 2H), 2.60 (s, 3H).

The compounds listed in Table 2 below were prepared using procedures analogous to those described above for the synthesis of Compound 2A-1 using the appropriate starting materials which are available commercially, prepared using preparations well-known to those skilled in the

art, or prepared in a manner analogous to routes described above for other intermediates.

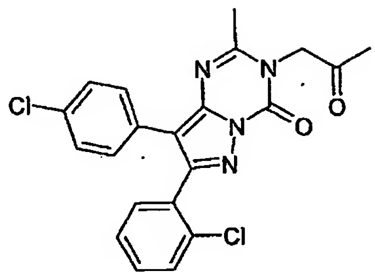
Table 2



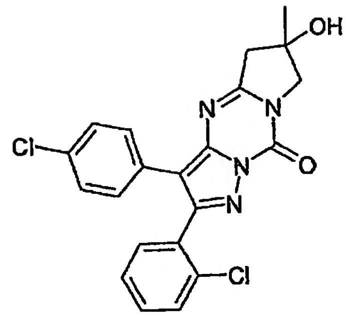
Example No.	$-R^2$	$-R^3$	$-R^4$	MS $(M+H)^+$
2A-2		H	$-CH_2CF_3$	453.3
2A-3		Me	$-CH_2CF_3$	445.2
2A-4		Me	$-CH_2CF_3$	433.2

Example 3

Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3-(2-oxo-propyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (3A-1) and 3-(4-Chlorophenyl)-2-(2-chlorophenyl)-6-hydroxy-6-methyl-6,7-dihydro-5H-1,4,7a,8a-tetraaza-s-indacen-8-one (3A-2):



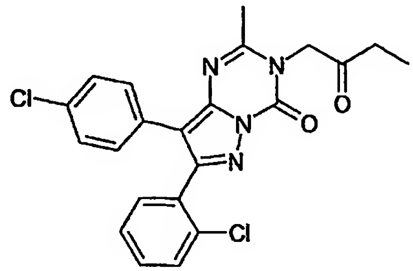
3A-1



3A-2

To a solution of 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3e; 100 mg, 0.27 mmol) in dimethylformamide (1 ml) was added Cs_2CO_3 (88 mg, 0.27 mmol) and then chloroacetone (22 µl, 0.27 mmol). After stirring overnight, the heterogeneous mixture was diluted with ethyl acetate and water. The precipitate was collected by filtration and washed with ethyl acetate to give 7-(2-chloro-phenyl)-8-(4-chlorophenyl)-3-(2,2-difluoropropyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (3A-1) as a colorless solid (43 mg, 37%). The water layer was extracted with ethyl acetate and the combined organic layers were washed with water and brine, dried ($MgSO_4$) and then concentrated, *in vacuo*, to afford the crude product (41 mg). Purification on a Chromatotron (loaded in THF) using 9:1 methylene chloride/hexanes, then 40-25:1 methylene chloride/ethanol as eluant afforded additional 3A-1 (23 mg, 20%) followed by 3A-2 (5 mg, 4%) as a solids. 3A-1: +ESI MS (M+1) 427.4; ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.40 (m, 4H), 7.35 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 5.16 (s, 2H), 2.47 (s, 3H), 2.35 (s, 3H). 3A-2: +ESI MS (M+1) 427.4; ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.40 (m, 4H), 7.33 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 9.1 Hz, 2H), 4.17 (dd, J = 11.6, 1.0 Hz, 2H), 4.05 (d, J = 11.6 Hz, 2H), 3.28 (d, J = 17.4 Hz, 2H), 3.06 (dd, J = 17.4, 1.0 Hz, 2H), 1.57 (s, 3H).

Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3-(2-oxo-butyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (3A-3):

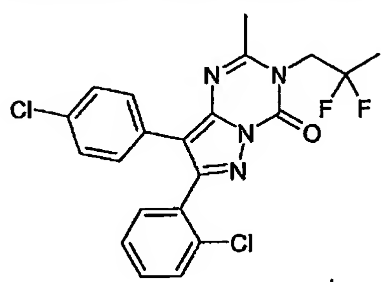


3A-3

7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3-(2-oxobutyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (3A-3) was prepared from 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3e) using procedures analogous to those described above for the synthesis of Compound 3A-1: +ESI MS (M+1) 441.4.

Example 4

Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-3-(2,2-difluoropropyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (4A-1):

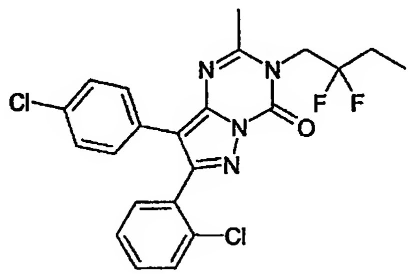


4A-1

To a suspension of 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3-(2-oxopropyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (3A-1; 43 mg, 0.10 mmol) in methylene chloride (1 ml) was added (diethylamino)sulfur trifluoride (150 µl, 1.1 mmol). After stirring overnight, the heterogeneous mixture was directly purified on a Biotage™ Flash 12S column using 20 to 30% ethyl acetate in hexanes as eluant to afford 4A-1 (12 mg, 27%) as a solid: +ESI MS (M+1) 449.4; ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.40 (m, 4H), 7.35 (d, *J*

= 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 4.69 (t, *J* = 13.1 Hz, 2H), 2.68 (s, 3H), 1.79 (t, *J* = 12.7 Hz, 3H).

<u>Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-3-(2,2-difluorobutyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (4A-2):</u>

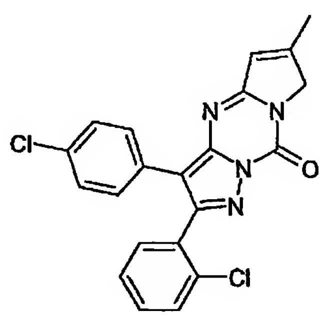


4A-2

7-(2-Chlorophenyl)-8-(4-chlorophenyl)-3-(2,2-difluorobutyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (3A-3) was prepared from 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3-(2-oxobutyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (3A-3) using procedures analogous to those described above for the synthesis of Compound 4A-1: +ESI MS (M+1) 463.4.

Example 5

<u>Preparation of 3-(4-Chlorophenyl)-2-(2-chlorophenyl)-6-methyl-7H-1,4,7a,8a-tetraaza-s-indacen-8-one (5A-1):</u>



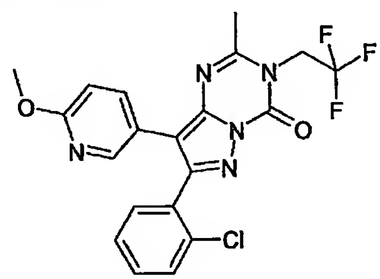
5A-1

To a solution of 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-1A-3e; 250 mg, 0.673 mmol) in

dimethylformamide (2 ml) was added Cs_2CO_3 (219 mg, 0.67 mmol) and then chloroacetone (54 µl, 0.67 mmol). After stirring for 7 days, additional Cs_2CO_3 (219 mg, 0.67 mmol) was added and the mixture was stirred for 2 more days. The heterogeneous mixture was diluted with ethyl acetate and water. The precipitate was collected by filtration and washed with ethyl acetate to give 3-(4-Chlorophenyl)-2-(2-chlorophenyl)-6-methyl-7H-1,4,7a,8a-tetraaza-s-indacen-8-one (5A-1) as a colorless solid (30 mg, 11%): +ESI MS (M+1) 409.4; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.53-7.48 (m, 1H), 7.45-7.37 (m, 3H), 7.35 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 6.39 (s, 1H), 4.72 (s, 2H), 2.28 (s, 3H).

Example 6

Preparation of 7-(2-Chlorophenyl)-8-(6-methoxypyridin-3-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (6A-1):



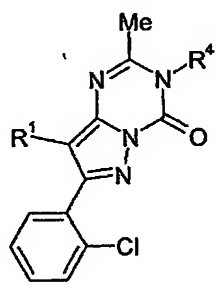
6A-1

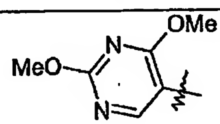
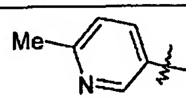
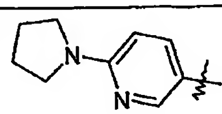
A mixture of 7-(2-chlorophenyl)-8-iodo-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-6A-1a; 80 mg, 0.17 mmol), (6-methoxy-3-pyridinyl)boronic acid (39 mg, 0.26 mmol), K_2CO_3 (47 mg, 0.34 mmol) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II), dichloromethane complex (7 mg, 0.008 mmol) was suspended in degassed dimethoxyethane (1.4 ml) and water (0.3 ml). The reaction was heated at 85 °C for 4 hours, cooled, and then diluted with ethyl acetate and filtered through Celite®. The organic solution was washed with water, saturated aqueous sodium bicarbonate, 0.02 M aqueous HCl, and then brine. After

drying ($MgSO_4$), the mixture was concentrated, *in vacuo*, and then purified on a Chromatotron using 0-30% ethyl acetate in methylene chloride as eluant to afford product 6A-1 as a solid (23 mg, 30%): +APcl MS (M+1) 450.0; ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, *J* = 2.5 Hz, 1H), 7.69 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.55-7.43 (m, 4H), 6.72 (d, *J* = 8.7 Hz, 1H), 5.02 (q, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 2.69 (s, 3H).

The compounds listed in Table 3 below were prepared using procedures analogous to those described above for the synthesis of Compound 6A-1 using the appropriate starting materials which are available commercially, prepared using preparations well-known to those skilled in the art, or prepared in a manner analogous to routes described above for other intermediates.

Table 3

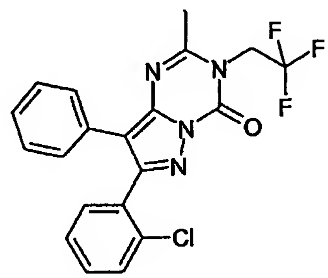


Example No.	-R^1	-R^4	MS $(M+H)^+$
6A-2		$-CH_2CF_3$	481.2
6A-3		$-CH_2CF_3$	434.2
6A-4		$-CH_2CF_3$	489.2

Example 7

Preparation of 7-(2-Chlorophenyl)-2-methyl-8-phenyl-3-(2,2,2-trifluoroethyl)-

3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (7A-1):

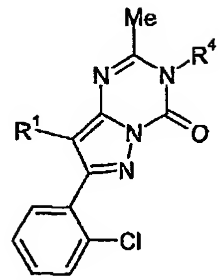


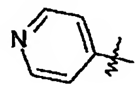
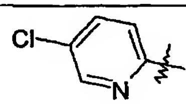
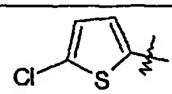
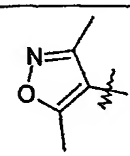
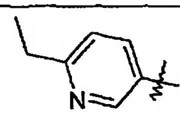
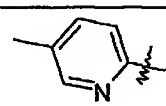
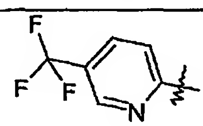
7A-1

To a mixture of 7-(2-chlorophenyl)-8-iodo-2-methyl-3-(2,2,2-trifluoro-ethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one (I-6A-1a; 100 mg, 0.213 mmol) and tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.010 mmol) was added trimethylstannyl benzene (150 mg, 0.622 mmol) in degassed DMF (1.5 ml). The reaction was heated at 105 °C for 18 hours under nitrogen, cooled and then diluted with ethyl acetate. The organic solution was washed with water and then brine. After drying ($MgSO_4$), the mixture was concentrated, *in vacuo*, and the resulting solid triturated from diethyl ether to afford product 7A-1 as a solid (40 mg, 45%): +ESI MS (M+1) 419.1; ^1H NMR (400 MHz, CD_3OD) δ 7.53-7.41 (m, 4H), 7.39-7.36 (m, 2H), 7.23-7.18 (m, 3H), 5.02 (q, J = 8.7 Hz, 2H), 2.69 (s, 3H).

The compounds listed in Table 4 below were prepared using procedures analogous to those described above for the synthesis of Compound 7A-1 using the appropriate starting materials which are available commercially, prepared using preparations well-known to those skilled in the art, or prepared in a manner analogous to routes described above for other intermediates.

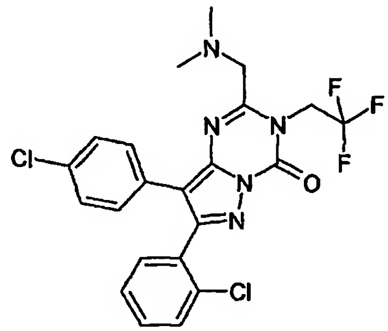
Table 4



Example No.	-R¹	-R⁴	MS (M+H)⁺
7A-2		$-CH_2CF_3$	420.2
7A-3		$-CH_2CF_3$	454.1
7A-4		$-CH_2CF_3$	459.1
7A-5		$-CH_2CF_3$	438.2
7A-6		$-CH_2CF_3$	448.2
7A-7		$-CH_2CF_3$	434.1
7A-8		$-CH_2CF_3$	488.1

Example 8

Preparation of 7-(2-Chlorophenyl)-8-(4-chlorophenyl)-2-((dimethylamino)methyl)-3-(2,2,2-trifluoroethyl)pyrazolo[1,5-a][1,3,5]triazin-4(3H)-one (8A-1):



8A-1

To a solution of 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-((dimethylamino)methyl)pyrazolo[1,5-a][1,3,5]triazin-4(3H)-one (I-8A-1e; 4 mg, 0.0097 mmol) in dimethylformamide (0.1 ml) at 0 °C was added Cs_2CO_3 (3 mg, 0.0097mmol) and trifluoromethanesulfonic acid 2,2,2-trifluoroethyl ester (2.2 mg, 0.0097 mmol). After warming to room temperature and stirring overnight, the mixture was extracted from water with ethyl acetate. The organic layer was concentrated, *in vacuo*, and then purified on a Chromatotron using 9.5:0.5:0.1 methylene chloride/ethyl acetate/methanol as eluant afforded 8A-1 (2.7 mg, 56%) as a solid: +ESI MS (M+1) 496.0; ^{1}H NMR (400 MHz, CD_3OD) δ 7.54-7.424 (m, 4H), 7.34 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 5.44 (q, J = 8.7 Hz, 2H), 3.68 (s, 2H) , 2.35 (s, 6H).

PHARMACOLOGICAL TESTING

The utility of the compounds of the present invention in the practice of the instant invention can be evidenced by activity in at least one of the protocols described herein below. The following acronyms are used in the protocols described below.

BSA - bovine serum albumin

DMSO - dimethyl sulfoxide

EDTA - ethylenediamine tetracetic acid

PBS – phosphate-buffered saline

EGTA - ethylene glycol-*bis*(β-aminoethyl ether) N,N,N',N'-tetraacetic acid

GDP - guanosine diphosphate

sc - subcutaneous

po - orally

ip - intraperitoneal

icv - intra cerebro ventricular

iv - intravenous

[^{3}H]SR141716A - radiolabeled N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride available from Amersham Biosciences, Piscataway, NJ.

[^{3}H]CP-55940 - radiolabled 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol available from NEN Life Science Products, Boston, MA.

AM251 - *N*-(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide available from Tocris™, Ellisville, MO.

Compounds having an activity <20 nM are generally tested in the CB-1 GTPγ [^{35}S] Binding Assay and the CB-2 binding assay described below in the Biological Binding Assays section. Selected compounds are then tested *in vivo* using one or more of the functional assays described in the Biological Functional Assays section below. The compounds in the Examples above provided a range of CB-1 receptor binding activities from 0.6 to 125 nM.

In Vitro Biological Assays

Bioassay systems for determining the CB-1 and CB-2 binding properties and pharmacological activity of cannabinoid receptor ligands are described by Roger G. Pertwee in "Pharmacology of Cannabinoid Receptor Ligands" Current Medicinal Chemistry, **6**, 635-664 (1999) and in WO 92/02640 (U.S. Application No. 07/564,075 filed August 8, 1990, incorporated herein by reference).

The following assays were designed to detect compounds that inhibit the binding of [^{3}H] SR141716A (selective radiolabeled CB-1 ligand) and [^{3}H] 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol; radiolabeled CB-1/CB-2 ligand) to their respective receptors.

Rat CB-1 Receptor Binding Protocol

PelFreeze brains (available from Pel Freeze Biologicals, Rogers, Arkansas) were cut up and placed in tissue preparation buffer (5 mM Tris HCl, pH = 7.4 and 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000 X g for 5 minutes at 4 °C. The supernatant was recovered and centrifuged at 100,000 X G for 1 hour at 4 °C. The pellet was then re-suspended in 25 ml of TME (25 nM Tris, pH = 7.4, 5 mM $MgCl_2$, and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [^{3}H] SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. A BCA protein assay was used to determine the appropriate tissue concentration and then 200 µl of rat brain tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 20 °C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

Human CB-1 Receptor Binding Protocol

Human embryonic kidney 293 (HEK 293) cells transfected with the CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in homogenization buffer (10 mM EDTA, 10 mM EGTA, 10

mM Na Bicarbonate, protease inhibitors; pH = 7.4), and homogenized with a Dounce Homogenizer. The homogenate was then spun at 1,000X g for 5 minutes at 4 °C. The supernatant was recovered and centrifuged at 25,000X G for 20 minutes at 4 °C. The pellet was then re-suspended in 10 ml of homogenization buffer and re-spun at 25,000X G for 20 minutes at 4 °C. The final pellet was re-suspended in 1 ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM $MgCl_2$ and 1 mM EDTA). A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [^{3}H] SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. The plates were covered and placed in an incubator at 30 °C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

<u>CB-2 Receptor Binding Protocol</u>

Chinese hamster ovary-K1 (CHO-K1) cells transfected with CB-2 cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in tissue preparation buffer (5 mM Tris-HCl buffer (pH = 7.4) containing 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000X g for 5 minutes at 4 °C. The supernatant was recovered and centrifuged at 100,000X G for 1 hour at 4 °C. The pellet was then re-suspended in 25 ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM $MgCl_2$ and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 10 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO, and 80.5% TME) and then 25 μl were added to the deep well polypropylene plate. [^{3}H] 5-(1,1-Dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol was diluted a ligand buffer (0.5% BSA and 99.5% TME) and then 25 μl were added to each well at a concentration of 1 nM. A BCA protein assay was used to determine the appropriate tissue concentration and 200 μl of the tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 30 °C for 60 minutes. At the end of the incubation period 250 μl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron format onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. The filters were then counted on the Wallac Betaplate™ counter.

CB-1 GTPγ [^{35}S] Binding Assay

Membranes were prepared from CHO-K1 cells stably transfected with the human CB-1 receptor cDNA. Membranes were prepared from cells as described by Bass et al, in "Identification and characterization of novel somatostatin antagonists," Molecular Pharmacology, **50**, 709-715 (1996). GTPγ [^{35}S] binding assays were performed in a 96 well FlashPlate™ format in duplicate using 100 pM GTPγ[^{35}S] and 10 μg membrane per well in assay buffer composed of 50 mM Tris HCl, pH 7.4, 3 mM $MgCl_2$, pH 7.4, 10 mM $MgCl_2$, 20 mM EGTA, 100 mM NaCl, 30 μM GDP, 0.1% bovine serum albumin and the following protease inhibitors: 100 μg/ml bacitracin, 100 μg/ml benzamidine, 5 μg/ml aprotinin, 5 μg/ml leupeptin. The assay mix was then incubated with increasing concentrations of antagonist (10^{-10} M to 10^{-5} M) for 10 minutes and challenged with the cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (10 μM). Assays were performed at 30 °C for one hour. The FlashPlates™ were then centrifuged at 2000Xg for 10 minutes. Stimulation of GTPγ[^{35}S] binding

was then quantified using a Wallac Microbeta. EC_{50} calculations done using Prism™ by Graphpad.

Inverse agonism was measured in the absense of agonist.

CB-1 FLIPR-based Functional Assay Protocol

CHO-K1 cells co-transfected with the human CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) and the promiscuous G-protein G16 were used for this assay. Cells were plated 48 hours in advance at 12500 cells per well on collagen coated 384 well black clear assay plates. Cells were incubated for one hour with 4 µM Fluo-4 AM (Molecular Probes) in DMEM (Gibco) containing 2.5 mM probenicid and pluronic acid (0.04%). The plates were then washed 3 times with HEPES-buffered saline (containing probenicid; 2.5 mM) to remove excess dye. After 20 min the plates were added to the FLIPR individually and fluorescence levels was continuously monitored over an 80 second period. Compound additions were made simultaneously to all 384 wells after 20 seconds of baseline. Assays were performed in triplicate and 6 point concentration-response curves generated. Antagonist compounds were subsequently challenged with 3 µM WIN 55,212-2 (agonist). Data were analyzed using Graph Pad Prism.

Detection of Inverse Agonists

The following cyclic-AMP assay protocol using intact cells was used to determine inverse agonist activity.

Cells were plated into a 96-well plate at a plating density of 10,000-14,000 cells per well at a concentration of 100 µl per well. The plates were incubated for 24 hours in a 37 °C incubator. The media was removed and media lacking serum (100 µl) was added. The plates were then incubated for 18 hours at 37 °C.

Serum free medium containing 1 mM IBMX was added to each well followed by 10 µl of test compound (1:10 stock solution (25 mM compound in DMSO) into 50% DMSO/PBS) diluted 10X in PBS with 0.1% BSA. After incubating for 20 minutes at 37 °C, 2 µM of Forskolin was added and then

incubated for an additional 20 minutes at 37 °C. The media was removed, 100 μl of 0.01N HCl was added and then incubated for 20 minutes at room temperature. Cell lysate (75 μl) along with 25 μl of assay buffer (supplied in FlashPlate™ cAMP assay kit available from NEN Life Science Products Boston, MA) into a Flashplate. cAMP standards and cAMP tracer were added following the kit's protocol. The flashplate was then incubated for 18 hours at 4 °C. The content of the wells were aspirated and counted in a Scintillation counter.

In Vivo Biological Assays

Cannabinoid agoinists such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenolhave been shown to affect four characteristic behaviors in mice, collectively known as the Tetrad. For a description of these behaviors see: Smith, P.B., et al. in "The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice." J. Pharmacol. Exp. Ther., **270**(1), 219-227 (1994) and Wiley, J., et al. in "Discriminative stimulus effects of anandamide in rats," Eur. J. Pharmacol., **276**(1-2), 49-54 (1995). Reversal of these activities in the Locomotor Activity, Catalepsy, Hypothermia, and Hot Plate assays described below provides a screen for *in vivo* activity of CB-1 antagonists.

All data is presented as % reversal from agonist alone using the following formula: (5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol/agonist - vehicle/agonist)/(vehicle/vehicle - vehicle/agonist). Negative numbers indicate a potentiation of the agonist activity or non-antagonist activity. Positive numbers indicate a reversal of activity for that particular test.

Locomotor Activity

Male ICR mice (n=6; 17-19 g, Charles River Laboratories, Inc., Wilmington, MA) were pre-treated with test compound (sc, po, ip, or icv). Fifteen minutes later, the mice were challenged with 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Twenty-five

minutes after the agonist injection, the mice were placed in clear acrylic cages (431.8 cm x 20.9 cm x 20.3 cm) containing clean wood shavings. The subjects were allowed to explore surroundings for a total of about 5 minutes and the activity was recorded by infrared motion detectors (available from Coulbourn Instruments™, Allentown, PA) that were placed on top of the cages. The data was computer collected and expressed as "movement units."

Catalepsy

Male ICR mice (n=6; 17-19 g upon arrival) were pre-treated with test compound (sc, po, ip or icv). Fifteen minutes later, the mice were challenged with 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Ninety minutes post injection, the mice were placed on a 6.5 cm steel ring attached to a ring stand at a height of about 12 inches. The ring was mounted in a horizontal orientation and the mouse was suspended in the gap of the ring with fore- and hind-paws gripping the perimeter. The duration that the mouse remained completely motionless (except for respiratory movements) was recorded over a 3-minute period.

The data were presented as a percent immobility rating. The rating was calculated by dividing the number of seconds the mouse remains motionless by the total time of the observation period and multiplying the result by 100. A percent reversal from the agonist was then calculated.

Hypothermia

Male ICR mice (n=5; 17-19 g upon arrival) were pretreated with test compounds (sc, po, ip or icv). Fifteen minutes later, mice were challenged with the cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Sixty-five minutes post agonist injection, rectal body temperatures were taken. This was done by inserting a small thermostat probe approximately 2- 2.5 cm into the rectum. Temperatures were recorded to the nearest tenth of a degree

Hot Plate

Male ICR mice (n=7; 17-19 g upon arrival) are pre-treated with test compounds (sc, po, ip or iv). Fifteen minutes later, mice were challenged with a cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Forty-five minutes later, each mouse was tested for reversal of analgesia using a standard hot plate meter (Columbus Instruments). The hot plate was 10" x 10" x 0.75" with a surrounding clear acrylic wall. Latency to kick, lick or flick hindpaw or jump from the platform was recorded to the nearest tenth of a second. The timer was experimenter activated and each test had a 40 second cut off. Data were presented as a percent reversal of the agonist induced analgesia.

Food Intake

The following screen was used to evaluate the efficacy of test compounds for inhibiting food intake in Sprague-Dawley rats after an overnight fast.

Male Sprague-Dawley rats were obtained from Charles River Laboratories, Inc. (Wilmington, MA). The rats were individually housed and fed powdered chow. They were maintained on a 12-hour light/dark cycle and received food and water *ad libitum*. The animals were acclimated to the vivarium for a period of one week before testing was conducted. Testing was completed during the light portion of the cycle.

To conduct the food intake efficacy screen, rats were transferred to individual test cages without food the afternoon prior to testing, and the rats were fasted overnight. After the overnight fast, rats were dosed the following morning with vehicle or test compounds. A known antagonist was dosed (3 mg/kg) as a positive control, and a control group received vehicle alone (no compound). The test compounds were dosed at ranges between 0.1 and 100 mg/kg depending upon the compound. The standard vehicle was 0.5% (w/v) methylcellulose in water and the standard route of administration was oral. However, different vehicles and routes of administration were used to accommodate various compounds when required. Food was provided to the

rats 30 minutes after dosing and the Oxymax automated food intake system (Columbus Instruments, Columbus, Ohio) was started. Individual rat food intake was recorded continuously at 10-minute intervals for a period of two hours. When required, food intake was recorded manually using an electronic scale; food was weighed every 30 minutes after food was provided up to four hours after food was provided. Compound efficacy was determined by comparing the food intake pattern of compound-treated rats to vehicle and the standard positive control.

Alcohol Intake

The following protocol evaluates the effects of alcohol intake in alcohol preferring (P) female rats (bred at Indiana University) with an extensive drinking history. The following references provide detailed descriptions of P rats: Li,T.-K., et al., "Indiana selection studies on alcohol related behaviors" in Development of Animal Models as Pharmacogenetic Tools (eds McClearn C. E., Deitrich R. A. and Erwin V. G.), Research Monograph 6, 171–192 (1981) NIAAA, ADAMHA, Rockville, MD; Lumeng, L, et al., "New strains of rats with alcohol preference and nonpreference" Alcohol And Aldehyde Metabolizing Systems, **3**, Academic Press, New York, 537–544 (1977); and Lumeng, L, et al., "Different sensitivities to ethanol in alcohol-preferring and -nonpreferring rats," Pharmacol. Biochem Behav., **16**, 125–130 (1982).

Female rats were given 2 hours of access to alcohol (10% v/v and water, 2-bottle choice) daily at the onset of the dark cycle. The rats were maintained on a reverse cycle to facilitate experimenter interactions. The animals were initially assigned to four groups equated for alcohol intakes: Group 1 - vehicle (n =8); Group 2 –positive control (e.g., 5.6 mg/kg AM251; n = 8); Group 3 – low dose test compound (n = 8); and Group 4 – high dose of test compound (n = 8). Test compounds were generally mixed into a vehicle of 30% (w/v) β-cyclodextrin in distilled water at a volume of 1-2 ml/kg. Vehicle injections were given to all groups for the first two days of the experiment. This was followed by 2 days of drug injections (to the appropriate groups) and a

final day of vehicle injections. On the drug injection days, drugs were given sc 30 minutes prior to a 2-hour alcohol access period. Alcohol intake for all animals was measured during the test period and a comparison was made between drug and vehicle-treated animals to determine effects of the compounds on alcohol drinking behavior.

Additional drinking studies were done utilizing female C57Bl/6 mice (Charles River). Several studies have shown that this strain of mice will readily consume alcohol with little to no manipulation required (Middaugh et al., "Ethanol Consumption by C57BL/6 Mice: Influence of Gender and Procedural Variables" Alcohol, 17 (3), 175-183, 1999; Le et al., "Alcohol Consumption by C57BL/6, BALA/c, and DBA/2 Mice in a Limited Access Paradigm" Pharmacology Biochemisrty and Behavior, 47, 375-378, 1994).

For our purposes, upon arrival (17-19 g) mice were individually housed and given unlimited access to powdered rat chow, water and a 10% (w/v) alcohol solution. After 2-3 weeks of unlimited access, water was restricted for 20 hours and alcohol was restricted to only 2 hours access daily. This was done in a manner that the access period was the last 2 hours of the dark part of the light cycle.

Once drinking behavior stabilized, testing commenced. Mice were considered stable when the average alcohol consumption for 3 days was ± 20% of the average for all 3 days. Day 1 of test consisted of all mice receiving vehicle injection (sc or ip). Thirty to 120 minutes post injection access was given to alcohol and water. Alcohol consumption for that day was calculated (g/kg) and groups were assigned (n=7-10) so that all groups had equivocal alcohol intake. On day 2 and 3, mice were injected with vehicle or drug and the same protocol as the previous day was followed. Day 4 was wash out and no injections were given. Data was analyzed using repeated measures ANOVA. Change in water or alcohol consumption was compared back to vehicle for each day of the test. Positive results would be interpreted as a compound that was able to significantly reduce alcohol consumption while having no effect on water

<u>Oxygen Consumption</u>

Methods:

Whole body oxygen consumption is measured using an indirect calorimeter (Oxymax from Columbus Instruments, Columbus, OH) in male Sprague Dawley rats (if another rat strain or female rats are used, it will be specified). Rats (300-380 g body weight) are placed in the calorimeter chambers and the chambers are placed in activity monitors. These studies are done during the light cycle. Prior to the measurement of oxygen consumption, the rats are fed standard chow ad libitum. During the measurement of oxygen consumption, food is not available. Basal pre-dose oxygen consumption and ambulatory activity are measured every 10 minutes for 2.5 to 3 hours. At the end of the basal pre-dosing period, the chambers are opened and the animals are administered a single dose of compound (the usual dose range is 0.001 to 10 mg/kg) by oral gavage (or other route of administration as specified, i.e., sc, ip, iv). Drugs are prepared in methylcellulose, water or other specified vehicle (examples include PEG400, 30% beta-cyclo dextran and propylene glycol). Oxygen consumption and ambulatory activity are measured every 10 minutes for an additional 1-6 hours post-dosing.

The Oxymax calorimeter software calculates the oxygen consumption (ml/kg/h) based on the flow rate of air through the chambers and difference in oxygen content at inlet and output ports. The activity monitors have 15 infrared light beams spaced one inch apart on each axis, ambulatory activity is recorded when two consecutive beams are broken and the results are recorded as counts.

Resting oxygen consumption, during pre- and post-dosing, is calculated by averaging the 10-min O_2 consumption values, excluding periods of high ambulatory activity (ambulatory activity count > 100) and excluding the first 5 values of the pre-dose period and the first value from the post-dose period. Change in oxygen consumption is reported as percent

and is calculated by dividing the post-dosing resting oxygen consumption by the pre-dose oxygen consumption *100. Experiments will typically be done with n = 4-6 rats and results reported are mean +/- SEM.

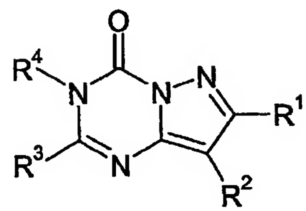
Interpretation:

An increase in oxygen consumption of >10% is considered a positive result. Historically, vehicle-treated rats have no change in oxygen consumption from pre-dose basal.

CLAIMS

What is claimed is:

1. A compound of Formula (I)



(I)

wherein

R^1 is an aryl optionally substituted with one or more substituents, or a heteroaryl optionally substituted with one or more substituents;

R^2 is R^{2a}, $-CH{=}CH{-}R^{2a}$, or $-CH_2CH_2{-}R^{2a}$, where R^{2a} is a chemical moiety selected from $(C_1\text{-}C_8)$alkyl, 3- to 8-membered partially or fully saturated carbocyclic ring(s), 3- to 6-membered partially or fully saturated heterocycle, aryl, or heteroaryl, where said chemical moiety is optionally substituted with one or more substituents;

R^3 is hydrogen or a chemical moiety selected from the group consisting of $(C_1\text{-}C_4)$alkyl, and $(C_1\text{-}C_4)$alkoxy, where said chemical moiety is optionally substituted with one or more substituents,

or R^3 taken together with R^4 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents; and

R^4 is a chemical moiety selected from the group consisting of $(C_1\text{-}C_8)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_4)$alkyl, a 3- to 8-membered partially or fully saturated carbocyclic ring(s), heteroaryl$(C_1\text{-}C_3)$alkyl, 5-6 membered lactone, 5- to 6-membered lactam, and a 3- to 6-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituents,

or R^4 taken together with R^3 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents,

provided that when R^3 is (C_3-C_4)alkyl, R^4 is not (2'-[1-(triphenylmethyl)-1H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl, or (2'-[1H-tetrazol-5-yl]-1,1'-biphenyl-4-yl)methyl;

a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

2. The compound of Claim 1 wherein

R^3 is hydrogen or (C_1-C_4)alkyl, where said (C_1-C_4)alkyl is optionally substituted with one or more substituents,

or R^3 taken together with R^4 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents; and

R^4 is a chemical moiety selected from the group consisting of (C_1-C_8)alkyl, aryl(C_1-C_4)alkyl, and 3- to 8-membered partially or fully saturated carbocyclic ring(s), where said chemical moiety is optionally substituted with one or more substituent;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

3. The compound of Claim 2 wherein

R^3 is hydrogen, fluoro-substituted (C_1-C_4)alkyl, or (C_1-C_4)alkyl, wherein said (C_1-C_4)alkyl is optionally substituted with (C_1-C_3)alkylamino, di((C_1-C_3)alkyl)amino, azetidine, pyrrolidine, piperidine, or morpholine, where said (C_1-C_3) alkyl is optionally substituted with one to three fluorines; and

R^4 is (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl, cyclopentyl or cyclohexyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

4. The compound of Claim 1 wherein R^3 is H, methyl, ethyl or trifluoromethyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

5. The compound of Claim 2 wherein R^3 is H, methyl, ethyl or trifluoromethyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

6. The compound of Claim 3 wherein R^3 is H, methyl, ethyl or trifluoromethyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

7. The compound of claim 3 which is

7-(2-chlorophenyl)-2-methyl-8-styryl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one.

8. The compound of Claim 1, 2, 3, 4, 5 or 6 wherein R^1 and R^2 are each independently a chemical moiety selected from phenyl, thiophenyl, pyridyl or pyrimidinyl, where said chemical moiety is substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

9. The compound of Claim 8 wherein R^1 is a phenyl substituted with one to three substituents independently selected from the group

consisting of halo, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl, and cyano; and

R^2 is phenyl, pyridyl, thiophenyl, or pyrimidinyl, where said phenyl, said pyridyl, said thienyl, and said pyrimidinyl are each substituted with one to three substituents independently selected from the group consisting of halo, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl, and cyano;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

10. The compound of Claim 9 wherein R^1 is 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-cyanophenyl, 2,4-dichlorophenyl, 4-chloro-2-fluorophenyl, 2-chloro-4-fluorophenyl, 2-methylphenyl, 2-chloro-4-methylphenyl, or 2,4-difluorophenyl; and

R^2 is 4-chlorophenyl, 4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-bromophenyl, 6-methylpyridin-3-yl, 6-ethylpyridin-3-yl, 6-methoxypyridin-3-yl, 5-chloropyridin-2-yl, 5-trifluoromethylpyridin-2-yl, 5-methylpyridin-2-yl, 5-chlorothiophen-2-yl, or 2,4-dimethoxypyrimidin-5-yl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

11. The compound of claim 10 selected from the group consisting of

7-(2-chlorophenyl)-8-(2,4-dimethoxypyrimidin-5-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-(2,2-difluoropropyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-(2,2-difluorobutyl)-2-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(6-methoxypyridin-3-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-ethyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(4-chlorophenyl)-3-methyl-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(5-chloropyridin-2-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-2-methyl-3-(2,2,2-trifluoroethyl)-8-(5-trifluoromethylpyridin-2-yl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one;

7-(2-chlorophenyl)-8-(5-chlorothiophen-2-yl)-2-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrazolo[1,5-a][1,3,5]triazin-4-one; and

7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-((dimethylamino)methyl)-3-(2,2,2-trifluoroethyl)pyrazolo[1,5-a][1,3,5]triazin-4(3H)-one;

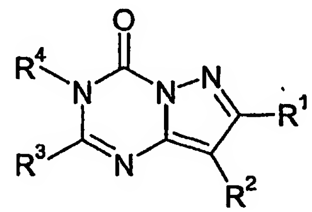
a pharmaceutically acceptable salt thereof, or a solvate or hydrate of the compound, or the salt.

12. A pharmaceutical composition comprising (1) a compound of any one of the preceding Claims, or a solvate or hydrate of said compound or said salt; and (2) a pharmaceutically acceptable excipient, diluent, or carrier.

13. The composition of Claim 12 further comprising at least one additional pharmaceutical agent selected from a nicotine receptor partial agonist, an opioid antagonist, a dopaminergic agent, an attention deficit activity disorder agent, or an anti-obesity agents.

14. A method for treating a disease, condition or disorder which is modulated by a cannabinoid receptor antagonist in animals comprising the

step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of Formula (I);



(I)

wherein

R^1 is an aryl optionally substituted with one or more substituents, or a heteroaryl optionally substituted with one or more substituents;

R^2 is aryl optionally substituted with one or more substituents, heteroaryl optionally substituted with one or more substituents, –CH=CH-R^{2a}, or –CH_2CH_2-R^{2a}, where R^{2a} is hydrogen or a chemical moiety selected from (C_1-C_8)alkyl, 3- to 8-membered partially or fully saturated carbocyclic ring(s), 3- to 6-membered partially or fully saturated heterocycle, aryl, heteroaryl, where the chemical moiety is optionally substituted with one or more substituents;

R^3 is hydrogen, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, or (C_1-C_4)alkoxy,

or R^3 taken together with R^4 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents; and

R^4 is a chemical moiety selected from the group consisting of (C_1-C_8)alkyl, aryl, heteroaryl, aryl(C_1-C_4)alkyl, a 3- to 8-membered partially or fully saturated carbocyclic ring(s), heteroaryl(C_1-C_3)alkyl, 5-6 membered lactone, 5- to 6-membered lactam, and a 3- to 6-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituents,

or R^4 taken together with R^3 forms a nitrogen containing 5- to 6-membered partially or fully saturated heterocyclic ring optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

15. The use of a compound of Claim 1 in the manufacture of a medicament for treating a disease, condition or disorder which is modulated by a cannabinoid receptor antagonist.

INTERNATIONAL SEARCH REPORT

International Application No
/IB2004/003673

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/53 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 2005	25/04/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fritz, M

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